

MODELLING THE IMMUNE SYSTEM  
TOOLBOX: STOCHASTIC REACTION MODELS

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January 16, 2007

This text is intended for **self-study**. It contains many **inline questions**; I invite the alert readers to try and answer the questions as they read.

QUESTION 0.0.1. *Where is the answer to an inline question ?*

1

Every chapter contains a **review section** that summarizes the main points and also contains further inline questions. The **exercise section** can be used as assignments in a lecture. The solutions are available on request; if time permits, a solution manual will eventually be available. The **Index** collects all terms and expressions that are highlighted in the text like *this* and also serves as a notation list.

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<sup>1</sup>In a chapter at the end.

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**2 Solutions**

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# CHAPTER 1

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## STOCHASTIC REACTION MODEL

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The stochastic reaction model is a special case of Markov process, and is the basis for many models used in the literature.

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## 1.1 MARKOV PROCESS ON COUNTABLE SPACE

### 1.1.1 DEFINITION

A *Markov process* is a stochastic process in continuous time, i.e. a function of time  $X(t)$  that is random and takes values in some space  $\mathcal{S}$ . We assume in this section that the state space is discrete (= countable); typically, it is a subset of  $\mathbb{N}^S$  for some integer  $S$ . A *Markov process* is one that has the property that the distribution of the process is entirely determined by its present state; in other words, if we want to simulate the process, the state description contains all information about the past that is needed to continue the simulation.

Being Markov is not a property of the real biological system, but rather, of the model that we make of it. A synonym for Markov process is *Continuous Time Markov Chain*.

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**EXAMPLE 1.1: IMMIGRATION-DEATH PROCESS.** This process is also called the  $M/M/\infty$  queue in queuing theory. The process counts the number of individuals in some species:  $X(t) \in \mathbb{N}$  (Figure 1.1).

Individuals arrive (immigrate) according to a Poisson process of rate  $\lambda$ . You can think of a Poisson process as the continuous time limit of the following discrete time process: at every time slot, flip a coin and decide whether an arrival occurs, independently of any past events. The coin is biased such that the probability that an arrival occurs in a time slot of duration  $\lambda$  is  $\lambda dt$ . The parameter  $\lambda$  is the rate of arrival, i.e. the average number of arrivals per time unit (it is the inverse of a time).

Individuals stay in the system for a random time, which in average has a duration  $\frac{1}{\mu}$ . More precisely, the distribution of the sojourn time is exponential, with rate  $\mu$ , and is drawn independently of all past. You can think of the exponential distribution as the as the continuous time limit of the following discrete time distribution: at every time slot (of duration  $dt$ ), flip a coin and decide, with probability  $\mu dt$ , whether the sojourn time expires. The parameter  $\mu$  is also a time inverse. One also sometimes uses the *half-life*, which is the median of the distribution of sojourn time and is equal to  $\frac{\ln(2)}{\mu}$ .

**QUESTION 1.1.1.** *Show this*

The process  $X(t)$  is Markov because both the Poisson process and the exponential distribution are memoryless.

---



QUESTION 1.1.2. *Modify Example 1.1 on page 2 and assume that the sojourn time is constant instead of exponentially distributed. Is  $X(t)$  still a Markov process ?*

In addition, we consider only Markov processes that are **time homogeneous**, i.e. their evolution does not depend on time (but only on the current state).

## 1.1.2 PROPERTIES

The main properties of a Markov process on a discrete space are the following.

1. There exists an array of numbers  $A_{i,j}$  (**transition rate matrix**, also called **generator**), where  $i, j$  are possible states of the process, such that, for any  $i \neq j$ :

$$\mathbb{P}\{X(t + dt) = j | X(t) = i\} = A_{i,j}dt + o(dt) \quad (1.1)$$

where  $o(dt)$  means some function of  $dt$  that goes to 0 more rapidly than  $dt$  (i.e.  $\lim_{dt \rightarrow 0} \frac{o(dt)}{dt} = 0$ ).  $A_{i,j}$  is called the **rate of transition from state  $i$  to state  $j$** . You can think of it as the conditional probability that the process will jump to state  $j$  in the next  $dt$  seconds, given that it is in state  $i$  now.

2. By convention, one usually lets

$$A_{i,i} = - \sum_{j \neq i} A_{i,j} \quad (1.2)$$

and we have (probability of no transition)

$$\mathbb{P}\{X(t + dt) = i | X(t) = i\} = 1 + A_{i,i}dt + o(dt) \quad (1.3)$$

3. The probability that two transitions occur **simultaneously** in the next  $dt$  seconds is  $o(dt)$ , i.e. can be neglected.

---

EXAMPLE 1.2: **IMMIGRATION-DEATH PROCESS**. The probability that an immigration occurs in the next  $dt$  seconds is  $\lambda dt$ , thus

$$\mathbb{P}\{X(t + dt) = n + 1 | X(t) = n\} = \lambda dt + o(dt)$$

The probability that a given individual leaves in the next  $dt$  seconds is  $\mu dt + o(dt)$ . If there are  $n$  individuals present in the system, the probability of **some** departure is  $1 - (1 - \mu dt - o(dt))^n = n\mu + o(dt)$ . Thus

$$\mathbb{P}\{X(t + dt) = n - 1 | X(t) = n\} = n\mu dt + o(dt)$$

and the formula is also true in the special case where  $n = 0$ . The transition rate matrix of the immigration death process is thus.

$$A = \begin{pmatrix} -\lambda & \lambda & 0 & 0 & \dots \\ \mu & -\lambda - \mu & \lambda & 0 \dots & \\ 0 & 2\mu & -\lambda - 2\mu & \lambda & \dots \\ 0 & 0 & 3\mu & -\lambda - 3\mu & \dots \\ \dots & \dots & \dots & \dots & \dots \end{pmatrix} \quad (1.4)$$

In theory, we know everything about such processes. For example, the probability distribution at time  $t$  is given by

$$\mathbb{P}(X(t) = i) = (\pi(0)e^{tA})_i \quad (1.5)$$

where  $\pi(0)$  is the row vector of initial probability distribution, i.e.  $\mathbb{P}\{X(0) = i\} = \pi_i(0)$ . The exponential  $e^{tA}$  in the formula is a matrix exponential. For more details on matrix exponentials, see for example in Wikipedia. It is a matrix of same dimensions as  $A$ , and has the property that  $e^{(t+s)A} = e^{sA}e^{tA} = e^{tA}e^{sA}$ . It gives the  $t$ -seconds ahead transition probabilities: for any  $t \geq 0$

$$(e^{tA})_{i,j} = \mathbb{P}\{X(t) = j | X(0) = i\} \quad (1.6)$$

QUESTION 1.1.3. Give an approximation of  $(e^{tA})_{i,j}$  valid for small values of  $t$ . (Hint: use Equation (1.1) and Equation (1.3))

When the state space is not too large, the matrix exponential can be computed and one can (numerically) compute all quantities of interest. However in most practical cases in our setting, the state space is huge. Consider for example a population of  $k$  different types of cells or molecules. The process is  $X(t) = (X_1(t), \dots, X_k(t))$ ; the state space has  $M^k$  states, where  $M$  is the maximum population count. With  $k = 10$  population types with  $M = 100$  max individuals per type, this is  $100^{10} = 10^{20}$ . This is why most papers resort to simulation.

### 1.1.3 LONG RUN BEHAVIOUR

There are also simple results for the large time limit behaviour of Markov processes.

An important feature of the Markov process is whether the state space is *irreducible*, i.e. any state can be reached in a number of transitions from any state. Assume that this is the case. If, in addition, the state space is finite, then the distribution of state space tends to a limiting probability  $\pi^*$ , i.e.  $\lim_{t \rightarrow +\infty} \mathbb{P}(X(t) = i) = \pi^*(i)$ . The limiting probability satisfies the balance equation

$$\pi^* A = 0 \quad (1.7)$$

and is uniquely defined by this set of equations (up to a multiplicative constant). If the state space is countable but infinite, one requires in addition a stability condition (the system does not “explode”). A necessary and sufficient condition for stability is the existence of some solution  $\nu$  of the balance equation (i.e.  $\nu A = 0$ ) such that  $\sum_{i \in \mathcal{S}} |\nu_i| < +\infty$  and  $\nu$  is non identically 0. If so, the limiting probability is  $\pi_i^* = \frac{\nu_i}{\sum_{j \in \mathcal{S}} \nu_j}$ .

If the state space is not irreducible, then the graph of transitions allows to classify the states as either *transient* or *recurrent*. A transient state is one such that it is possible to start a path of transitions from this state that makes any return impossible (in any finite number of transitions). A non transient state is recurrent. The set of recurrent states can be partitioned in *recurrence classes*, i.e. maximal subsets in which one can go from any state to any other state in a finite number of transitions (see Figure ??). Note that for this classification, the only thing that matters is whether a transition rate is 0 or not; the values of the non zero transition rates does not matter. The state space is irreducible if and only if all states are recurrent and there is only one recurrence class. If the state space is not irreducible, then after some (random) time the process will visit one randomly chosen recurrence class and will stay in it forever. In such cases the balance equation

Equation (1.7) has one solution (up to a multiplicative constant) per recurrence class and any combination of these solutions is a solution.

---

**EXAMPLE 1.3: IMMIGRATION-DEATH PROCESS.** It is easy to see that the state space is irreducible. The balance equation is:

$$\nu_i(\lambda + i\mu) = \nu_{i-1}\lambda + \nu_{i+1}(i+1)\mu \text{ for } i = 1, 2, \dots \quad (1.8)$$

$$\nu_0\lambda = \nu_1\mu \quad (1.9)$$

which we can interpret by saying that the rate of probability of leaving state  $i$  is equal to the rate of probability of reaching state  $i$ . This system of equations can be solved iteratively starting from  $i = 0$ , assuming  $\nu_0 = 1$  (which we can do without loss of generality since a solution of the balance equation is known up to a multiplicative constant). One obtains

$$\nu_i = \frac{\lambda^i}{i!\mu^i}$$

It follows that the sum

$$\sum_{i=0}^{+\infty} \nu_i = e^{\frac{\lambda}{\mu}} < +\infty$$

thus the system is stable for any values of  $\lambda$  and  $\mu$ , and the limiting probability distribution is

$$\pi_i^* = \frac{\lambda^i}{i!\mu^i} e^{-\frac{\lambda}{\mu}}$$

This is the Poisson distribution, with mean  $\frac{\lambda}{\mu}$ .

Figure 1.1 shows a simulation of this process. We see that, after some transient time, the process tends to become distributed around the mean value  $\frac{\lambda}{\mu}$ .

---

## 1.2 STOCHASTIC REACTION MODEL

The *Stochastic Reaction Model* is a way of compressing the description of a Markov process, which is well suited to modelling biological systems. It originates from chemistry, from where it borrows some elements of terminology.

### 1.2.1 DEFINITION

In order to specify a Markov process, one can give the transition rate matrix  $A$ . For complicated processes, this is a huge array. One can compress the description by exploiting some structure in the process.

**DEFINITION 1.2.1.** *A stochastic reaction model is a description of a Markov process based on the following framework.*

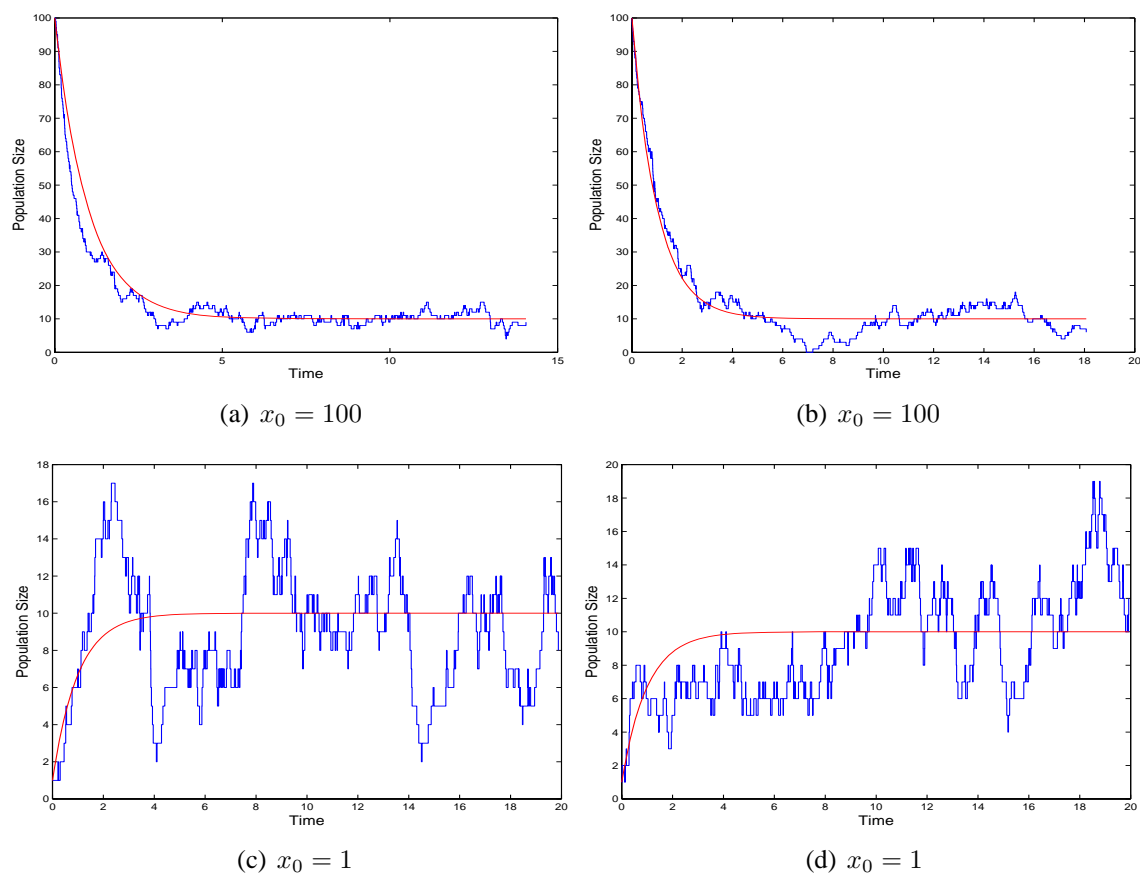


Figure 1.1: Four independent simulation runs of the Immigration Death process with  $\lambda = 10$  and  $\mu = 1$  and two sets of initial conditions ( $x_0$ ). The plain line is the exact value of  $\mathbb{E}(X(t))$ .

1. The set of possible states  $\mathcal{S}$  is a subset of  $\mathbb{N}^S$  for some integer  $S$ . In other words, the state at time  $t$  has the form

$$\vec{X}(t) = (X_1(t), \dots, X_s(t), \dots, X_S(t)) \quad (1.10)$$

where  $X_s(t)$  is interpreted as the number of individuals in species  $s$ .

2. There are  $R$  **reactions**, each associated with a change in the population. When reaction  $r$  occurs, the state changes from  $\vec{x}$  to  $\vec{x} + \vec{\Delta}_r$ . The vector  $\vec{\Delta}_r$  is called the **effect** of reaction  $r$ .
3. (**Rate function:** ) The rate of transition of reaction  $r$  is a function  $h_r(\cdot)$ . The value  $h_r(\vec{x})$  is the probability that a reaction of type  $r$  occurs in the next  $dt$  seconds, given that  $\vec{X}(t) = \vec{x}$ .
4. To avoid inconsistencies, we assume that reactions cannot lead to impossible states: If  $\vec{x} + \vec{\Delta}_r(\vec{x}) \notin \mathcal{S}$  then  $h_r(\vec{x}) = 0$ .

The rate function  $h_r(\cdot)$  is called **propensity** in chemistry or **hazard rate** in finance.

---

EXAMPLE: **IMMIGRATION-DEATH PROCESS**. There are  $S = 1$  species and  $R = 2$  reactions ("arrival", "departure"). The state space is  $\mathcal{S} = \mathbb{N}$ .

Reaction	Effect	Rate
1 (arrival)	$\vec{\Delta}_1 = +1$	$h_1(x) = \lambda$
2 (departure)	$\vec{\Delta}_2 = -1$	$h_2(x) = x\mu$

The **transition rate** matrix of a stochastic reaction model is given by the following formulas:

$$A(\vec{x}, \vec{x} + \vec{\Delta}_r(\vec{x})) = h_r(\vec{x}) \quad (1.11)$$

$$A(\vec{x}, \vec{x}') = 0 \text{ if for all } r \ \vec{x} + \vec{\Delta}_r(\vec{x}) \neq \vec{x}' \quad (1.12)$$

$$A(\vec{x}, \vec{x}) = - \sum_r h_r(\vec{x}) \quad (1.13)$$

Note that there is not much loss of generality when considering stochastic reaction models: any arbitrary Markov process on a finite space  $\mathcal{S} \subset \mathbb{N}^I$  can be described as a stochastic reaction model.

QUESTION 1.2.1. Show how an arbitrary Markov process on a finite space can be described as a stochastic reaction model.

### 1.2.2 EXAMPLE: IMMUNE RESPONSE MODEL

This example is the stochastic version of the model in [2]. It represents a population of target cells, infected by a virus, in presence of an immune response. The state is  $X = (T, I, E)$  where

- $T$ = population of target cells;
- $I$ = population of infected cells;
- $E$ = population of effectors (immune response).

The state space is  $\mathcal{S} = \mathbb{N}^3$ . There are  $S = 3$  species and  $R = 7$  reactions. The effects are described below.

Reaction	Description	Effect	Rate
1	Influx of New Target Cells	$T := T + 1$	$\sigma$
2	Infection	$I := I + 1; T := T - 1$	$\beta TI$
3	Elimination of Infected Cell	$I := I - 1$	$kIE$
4	Proliferation of Effectors	$E := E + 1$	$\alpha IE$
5	Death of target cells	$T := T - 1$	$\delta_T T$
6	Death of infected cells	$I := I - 1$	$\delta_I I$
7	Death of effector cells	$E := E - 1$	$\delta_E E$

Reaction 1 has a constant rate because it is assumed that there is a generation of healthy cells (probably from stem cells) at a rate not affected by the infection. Reactions 2,3 and 4 have a rate proportional to two populations, as they represent the results of binary interactions. Reactions 5, 6 and 7 represent death processes have a rate proportional to the population of interest.

In this description we used a different convention to describe the effects. Instead of giving the effects  $\vec{\Delta}_r$ , we give the result of applying the reaction to the state vector  $(T, I, E)$ , by writing only those coordinates that are affected. An alternative method would have been to describe the effects, as follows.

Reaction $r$	Effect $\vec{\Delta}_r$
1	(+1, 0, 0)
2	(-1, +1, 0)
3	(0, -1, 0)
4	(0, 0, +1)
5	(-1, 0, 0)
6	(0, -1, 0)
7	(0, 0, -1)

Figure 1.2 shows a few simulation runs.

QUESTION 1.2.2. *Comment on the variability of the  $X(t)$  from one run to the other.*

To analyze the **long run behaviour** of this model we first classify the states. A state is a triple  $(t, i, e) \in \mathbb{N}^3$ . We need to determine the graph of state transitions; it is derived from the rules in the tables above. The possible transitions are given in the tables below. For  $i > 0$  the transitions are:

	from $\rightarrow$ to	additional condition	reaction number
1	$t, i, e \rightarrow t - 1, i, e$	$t > 0$	5
2	$t, i, e \rightarrow t + 1, i, e$		1
3	$t, i, e \rightarrow t, i - 1, e$		3,6
4	$t, i, e \rightarrow t - 1, i + 1, e$	$t > 0$	2
5	$t, i, e \rightarrow t, i, e - 1$	$e > 0$	7
6	$t, i, e \rightarrow t, i, e + 1$		4

and for  $i = 0$ :

	from $\rightarrow$ to	additional condition	reaction number
7	$t, 0, e \rightarrow t - 1, 0, e$	$t > 0$	5
8	$t, 0, e \rightarrow t + 1, 0, e$		1
9	$t, 0, e \rightarrow t, 0, e - 1$	$e > 0$	7

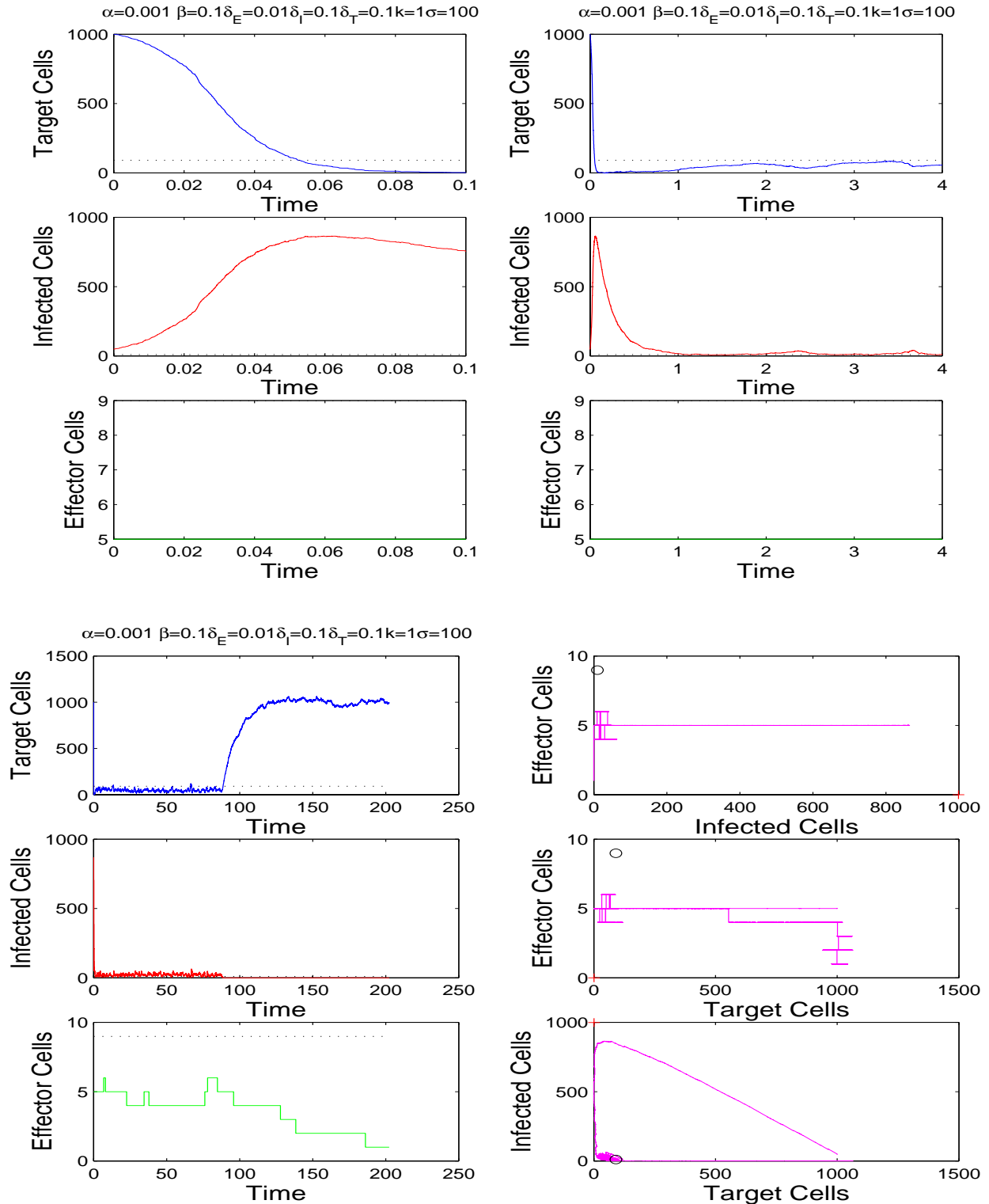


Figure 1.2: One simulation run of the Immune response model in Section 1.2.2. Initial values:  $T(0) = 1000$ ,  $I(0) = 50$  and  $E(0) = 5$ . The time axis is in days. Parameter values are  $\alpha = 0.001$ ,  $\beta = 0.1$ ,  $\delta_E = 0.01$ ,  $\delta_I = 0.1$ ,  $\delta_T = 0.1$ ,  $k = 1$  and  $\sigma = 100$ . First three panels:  $T(t)$ ,  $I(t)$ ,  $E(t)$  as a function of time (time plots), for the same simulation run zoomed at three different time scales. Last panel:  $I(t)$  versus  $E(t)$ ,  $E(t)$  versus  $T(t)$  and  $I(t)$  versus  $T(t)$  (phase plots) for  $t \in [0, 200]$ . The circles are the non-trivial equilibrium predicted by the differential equation method in Section 1.5.

We see that if we start with  $i = 0$  we can never increase  $i$ . It follows that if we start from a state with  $i > 0$  there is a path that leads to some state with  $i = 0$ , from where we can never come back to the original state. Thus all states with  $i > 0$  are transient.

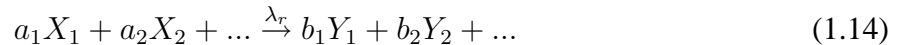
Now let us examine states  $(t, 0, e)$ ; from there we can only decrease  $e$ , except if  $e = 0$ ; thus these states are transient except for  $e = 0$ .

Finally from any state  $(t, 0, 0)$  we can go to any other state  $(t', 0, 0)$ , and only to such states. Thus there is one recurrence class; it made of all states with  $i = e = 0$ . To see if the system is stable we solve the balance equation assuming that  $\nu(t, i, e) = 0$  except if  $i = e = 0$ . These are the same equations as for the immigration-death process, thus the process is stable for any values of its parameters. But in the long run limit, it always (sooner or later) ends up with  $I(t) = E(t) = 0$ . The limiting distribution of the state  $(T, 0, 0)$  is obtained as in Example 1.3 on page 5, i.e.  $T$  is Poisson with mean  $\frac{\sigma}{\delta_T}$ .

### 1.2.3 STOCHASTIC REACTION NETWORKS

*Stochastic reaction networks* is a variant of stochastic reaction model. They were originally introduced to describe chemical reactions, but are used for other population models like we use for modelling the immune system.

A reaction network is a stochastic reaction model with  $S$  species and  $R$  reactions. Every reaction is written in a form



with the following convention.

- $X_i$  is an overloaded representation that means both “species  $i$ ” and the number of individuals of species  $i$
- Items on the left-handside are called *reactants*, on the right handside, *products*.
- A coefficient such as  $a_i$  or  $b_i$  is called a *stoichiometry*. The *effect* of reaction  $r$  is the difference between product stoichiometry and reactant stoichiometry.
- The *reaction rate* is given by  $\lambda_r$ . By default,  $\lambda_r$  is a constant and the reaction rate is given by

$$h_r = \lambda_r X_1^{a_1} X_2^{a_2} \dots \quad (1.15)$$

If the default rule in Equation (1.15) does not apply, then  $\lambda_r$  is a function of the reactant, given explicitly.

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EXAMPLE 1.4: **IMMUNE REACTION.** The Immune Reaction model can be alternatively described using the formalism of reaction networks, as follows.





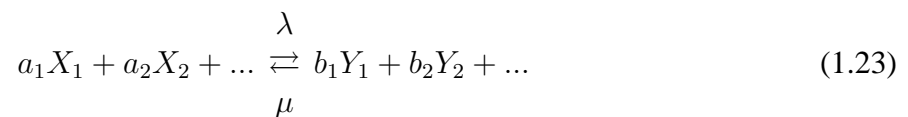
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QUESTION 1.2.3. *Does this reaction network describe exactly the same Markov process as the stochastic reaction model in Section 1.2.2 ?*

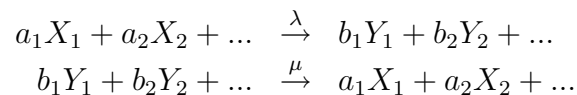
Reaction networks are implemented in formal description languages such as SBML (Systems Biology Markup Language) or the language TSED developed at EPFL. The default rules for the rate functions were shown by Gillespie to be valid for well stirred chemical reactions, and are generally accepted for many bio-chemical reactions.

Reaction networks provide our first examples of population models. By default, when population of cells or molecules interact according to Equation (1.14), and if there is no specific constraints, then the rates of the reactions are given by the default rule in Equation (1.15). The reactions of immigration, death and proliferation usually are in this case.

**Reversible reactions** are simply the conjunction of two independent reactions:



is the same as



## 1.2.4 OTHER CLASSICAL STOCHASTIC REACTIONS

### HOMEOSTATIC REGULATION

This a set of  $s$  reactions that models the fact that species  $1 \dots s$  share some common resource, or are subject to a regulation that tends to control the total population  $X_1 + \dots + X_s$ .

- Effect of reaction  $i$  ( $i = 1, \dots, s$ ):  $X_i := X_i - 1$
- Rate of reaction  $i$ :  $\lambda X_i (X_1 + \dots + X_k)$  where  $\lambda$  is some constant.

### MICHAELIS-MENTEN

This models reactions that use a catalyst, or enzymes. It is also applied to binding sites on dendritic cells. Assume a population  $X_1$  is transformed into another population  $Y_1$ , by a mechanism that involves a catalyst, or facilitator  $C$ . Assume one unit of population  $X_1$  needs to combine with one facilitator, for the reaction to occur. This is modeled by the following reaction:



with rate

$$h_1(X_1) = \frac{\lambda X_1}{X_1 + x_1^*} \quad (1.25)$$

The constant  $\lambda$  is the maximum value of the rate, reached when  $X_1$  is large. The constant  $x_1^*$  is the *Michaelis-Menten* constant; it is the value of  $X_1$  for which the rate is half its maximum value.

If 2 units of  $X_1$  need to combine with one facilitator, for the reaction to occur, the reaction is



and the rate now has the form

$$h_2(X_1) = \frac{\lambda X_1^2}{X_1^2 + (x_1^*)^2} \quad (1.27)$$

A similar case is with more than one reactants that bind to one or more facilitators:



The rate then has the form

$$h_3(X_1, X_2) = \frac{\lambda X_1 X_2}{k_0 + k_1 X_1 + k_2 X_2 + k_3 X_1 X_2} \quad (1.29)$$

In Section 1.6.1 we give an explanation for this model.

## 1.3 SIMULATION OF REACTION MODELS

### 1.3.1 GILLESPIE'S DIRECT METHOD

Simulating a reaction model means drawing a sample path, given some initial conditions. This is in principle simple, based on the following property.

**THEOREM 1.3.1.** *Consider a stochastic reaction network. Let  $T^+(t)$  be the time at which the next reaction occurs, counted from time  $t$ . Then*

1. *the conditional distribution of  $T^+(t) - t$ , given that  $\vec{X}(t) = \vec{x}_0$ , is exponential with parameter  $\sum_r h_r(\vec{x}_0)$*
2. *the conditional probability that the next reaction is reaction  $r_0$ , given that  $\vec{X}(t) = \vec{x}_0$ , is  $\frac{h_{r_0}(\vec{x}_0)}{\sum_r h_r(\vec{x}_0)}$*
3. *the time until next transition  $T^+(t) - t$  and the choice of the next reaction are conditionally independent, given that  $\vec{X}(t) = \vec{x}_0$ .*

---

**EXAMPLE 1.5: IMMIGRATION-DEATH PROCESS.** Given that there are  $n$  individuals present in the system, the distribution of time until next transition is exponential with rate  $\lambda + n\mu$ ; the probability that the next transition is an arrival is  $\frac{\lambda}{\lambda + n\mu}$ , that it is a departure is  $\frac{n\mu}{\lambda + n\mu}$ . The choice of the next event (arrival or departure) can be drawn independently of the time until next event.

The theorem gives us a means to generate the next transition step by step. The resulting simulation algorithm is called *Gillespie's Direct method*.

---

**Algorithm 1** Gillespie's Direct Method
 

---

```

1: procedure GILLESPIE( $T_{\max}, \vec{x}_0$ )
                                      $\triangleright T_{\max}$ : maximum duration of simulation
                                      $\triangleright \vec{x}_0$ : initial state
2:    $\vec{X} \leftarrow \vec{x}_0$ 
3:    $t = 0$ 
4:   loop
5:     draw  $T \sim \text{Expo} \left( \sum_r h_r(\vec{X}) \right)$ 
6:      $t := t + T$ 
7:     if  $t > T_{\max}$  then
8:       break
9:     end if
10:    draw  $R$  in set of reactions according to the probability distribution
         $\mathbb{P}\{R = r_0\} = \frac{h_{r_0}(\vec{X})}{\sum_r h_r(\vec{X})}$ 
11:     $\vec{X} \leftarrow \vec{X} + \Delta_R$ 
12:    output( $t, \vec{X}$ )
13:  end loop
14: end procedure

```

---

To apply Gillespie's direct method we need to be able to draw a sample of an exponential random variable (line 5). This can be done by using the fact that if  $U$  is a uniform random variable between 0 and 1, then  $\frac{-\ln(U)}{\lambda}$  is distributed according to the exponential distribution with rate  $\lambda$ . The random variable  $U$  is sampled by calling the random number generator.

Similarly (line 10), in order to draw a random value in the finite set  $\{1, 2, \dots, r_{\max}\}$  with probabilities  $p_1, \dots, p_{\max}$  (where  $\sum_{r=1}^{r_{\max}} p_r = 1$ ), one draws a uniformly distributed number  $V \sim \text{Unif}(0, 1)$  and searches for the index  $r$  such that

$$P_{r-1} \leq V < P_r$$

where  $P_0 = 0$  and  $P_r = p_1 + \dots + p_r$  (see [3], chapter "Simulation" for explanations).

---

**EXAMPLE 1.6: IMMIGRATION-DEATH PROCESS.** A simulation code in matlab, using Gillespie's direct method, is given below.

```

function [] = imde(n,x0,la,mu) % immigration model simulation
% use it for example with imde(400,100,10,1)
% n=max simulation time in transitions
% x0 = initial population
% la =immigration rate
% mu = death rate
x= x0*ones(1,n); % x data

```

```

t= zeros(1,n); % times
for i=2:n
    rate = la + x(i-1)*mu;
    t(i)=t(i-1)-log(rand(1))/rate;
    v=rand(1);
    if (v < la/rate) % arrival
        x(i)=x(i-1)+1;
    else
        x(i)=x(i-1)-1;
    end
end
plot(t,x);
return

```

### 1.3.2 TIME STEPPED METHOD

The previous algorithm may become prohibitive if the state space is large, which is often true in practice. We will see later a number of fundamental simplifications that can be made to the model itself. Here, we discuss a simplification, and approximation, of the simulation algorithm. It is based on the following theorem.

**THEOREM 1.3.2.** *Consider a stochastic reaction model. Assume the rate  $h_{r_0}$  of some reaction  $r_0$  is independent of the state. The number of times that reaction  $r_0$  occurs in a time interval of duration  $t$  is Poisson with mean  $th_{r_0}$ .*

The idea of the time stepped method is to take a discrete time step  $\delta$  that is small enough so that the rates of all reactions do not vary much; of course,  $\delta$  needs to be large enough so that we do speed up the simulation. The following algorithm applies when the state space is  $\mathcal{S} = \mathbb{N}^S$  for some integer  $S$ .

Line 7 requires sampling from the Poisson distribution. This is more complicated than the sampling in the previous algorithm, but is readily implemented in statistical packages (see below for a Matlab example).

Line 8 sets  $\vec{X}_s$  to 0 if the update equation would produce a negative value. If the state space puts some constraints on  $\vec{X}$  other than being non-negative (for example  $X_s \leq x_s^{\max}$  for some  $s$ ) then one needs to modify line 8 accordingly.

One needs to validate the approximation made by the time stepped method, for example by reducing the time step  $\delta$  until there is no visible change in the simulation output.

The time stepped method can be refined: the time step  $\delta$  can be kept small at times when the rates vary rapidly, and large when rates vary much (Gillespie calls it the  $\tau$ -leap method). Also, it is possible to combine the direct method (to slow reactions) with the time-stepped (to fast reactions) [4].

---

**EXAMPLE 1.7: IMMIGRATION-DEATH PROCESS.** A simulation code in matlab, using the time stepped method, is given below. Sample outputs are shown in Figure 1.3

**Algorithm 2** Time Stepped Method

---

```

1: procedure TIMESTEPPED( $T_{\max}, \vec{x}_0, \delta$ )
                                     ▷  $T_{\max}$ : maximum duration of simulation
                                     ▷  $\vec{x}_0$ : initial state
                                     ▷  $\delta$ : time step

2:    $\vec{X} \leftarrow \vec{x}_0$ 
3:    $t = 0$ 
4:    $n_{\max} = \text{floor}(\frac{T_{\max}}{\delta})$ 
5:   for  $n \leftarrow 1, n_{\max}$  do
6:     for  $r \leftarrow 1, R$  do
7:       draw  $d_r \sim \text{Poisson}(\delta h_r(\vec{X}))$ 
8:        $\vec{X} \leftarrow \max(\vec{X} + \sum_r d_r \Delta_r, \vec{0})$ 
9:     end for
10:    output( $t, \vec{X}$ )
11:  end for
12: end procedure

```

---

```

function [] = imdets(tmax,x0,la,mu, delta)
    % immigration model simulation, time stepped version
    % tmax = max simulation time
    % x0 = initial population
    % la =immigration rate
    % mu = death rate
    % delta = time step

    n= floor(tmax/delta)
    x= x0*ones(1,n); % x data
    t= (0:(n-1))*delta; % times

    for i=2:n
        arrivals = poissrnd(la*delta);
        departs = poissrnd(mu*x(i-1)*delta);
        x(i)=max(x(i-1)+arrivals-departs,0);
    end

    % arrange plots for nice jump process
    arranget = zeros(n,2*n-1);
    arranget(1,1)=1;
    for j=1:(n-1)
        arranget(j+1,2*j)=1;
        arranget(j+1,2*j+1)=1;
    end
    arrangex = zeros(n,2*n-1);
    arrangex(n,2*n-1)=1;
    for j=1:(n-1)
        arrangex(j,2*j-1)=1;
        arrangex(j,2*j)=1;
    end

```

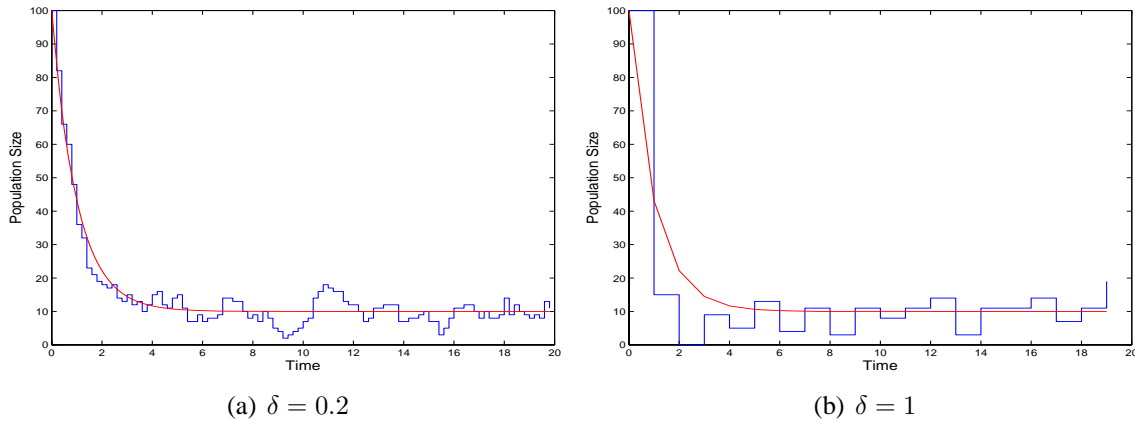


Figure 1.3: Two simulation runs of the Immigration Death process with  $\lambda = 10$  and  $\mu = 1$ , with the time stepped method ( $\delta = \text{time step}$ ). The plain line is the exact value of  $\mathbb{E}(X(t))$

```

end

plot(t*arranget,x*arrangex);
return

```

## 1.4 THE DRIFT EQUATION

Stochastic models are able to reproduce the “irregularity” of biological systems, but they can sometimes be simplified and replaced by deterministic models. The link is the drift equation of Markov processes, which we give in a form adapted to the stochastic reaction framework.

### 1.4.1 THE DRIFT EQUATION

**THEOREM 1.4.1.** *Consider a stochastic reaction model. For any function  $f()$  of the state space such that the expectations are well defined we have*

$$\frac{d}{dt} \mathbb{E} \left( f(\vec{X}(t)) \right) = \mathbb{E} \left( \text{drift of } f \text{ at } \vec{X}(t) \right) \quad (1.30)$$

where

$$\text{drift of } f \text{ at } \vec{x} = \sum_r h_r(\vec{x}) \left[ f(\vec{x} + \vec{\Delta}_r) - f(\vec{x}) \right]$$

The *drift equation* (1.30) contains essentially the same information as the properties in Section 1.1.2, but in a form more suitable to derive deterministic equations. The function  $f()$  in the theorem is a function of the state, therefore is defined on  $\mathcal{S} \subset \mathbb{N}^S$ .

**EXAMPLE 1.8: IMMIGRATION-DEATH PROCESS.** The state space is  $\mathcal{S} = \mathbb{N}$ . Let us take  $f(x) = x$ , for  $x \in \mathbb{N}$ . We have:

drift of  $f$  at  $x = \lambda - \mu x$

$$\frac{d}{dt} \mathbb{E}(X(t)) = \mathbb{E}(\lambda - \mu X(t)) = \lambda - \mu \mathbb{E}(X(t)) \quad (1.31)$$

Let  $\bar{x}(t) = \mathbb{E}(X(t))$ . The drift equation gives

$$\frac{d\bar{x}}{dt} = \lambda - \mu \bar{x} \quad (1.32)$$

This is an ordinary differential equation which can be solved into:

$$\bar{x}(t) = \frac{\lambda}{\mu} + \left( \bar{x}(0) - \frac{\lambda}{\mu} \right) e^{-\mu t} \quad (1.33)$$

We see that when  $t$  grows  $\bar{x}(t)$  approaches the limit  $\frac{\lambda}{\mu}$ . In Figure 1.1 and Figure 1.3 the value of  $\bar{x}(t)$  is plotted as a plain, red line.

QUESTION 1.4.1. *Is  $X(t)$  an integer?  $\bar{x}(t)$ ?*

## 1.4.2 THE MASTER EQUATION

The drift equation can be used to derive a set of differential equations for the probability distribution of state, called the *master equation* or forward-*Chapman-Kolmogorov* equation.

**THEOREM 1.4.2.** *For a stochastic reaction model:*

$$\begin{aligned} \frac{d}{dt} \mathbb{P}\{X(t) = \vec{x}_0\} &= \sum_r \mathbb{P}\{X(t) = \vec{x}_0 - \vec{\Delta}_r\} h_r(\vec{x}_0 - \vec{\Delta}_r) - \mathbb{P}\{X(t) = \vec{x}_0\} \sum_r h_r(\vec{x}_0) \\ &= \text{rate of proba of reaching state } \vec{x}_0 - \text{rate of proba of leaving state } \vec{x}_0 \end{aligned} \quad (1.34)$$

**Proof.** The master equation derives from the drift equation. To see why, consider some fixed state  $\vec{x}_0 \in \mathcal{S}$  and take for  $f$  the indicator function of  $\vec{x}_0$ . The drift of  $f$  at some arbitrary vector  $\vec{x}$  is:

$$\text{drift of } f \text{ at } \vec{x} = \sum_r h_r(\vec{x}) \left[ 1_{\{\vec{x} + \vec{\Delta}(r) = \vec{x}_0\}} - 1_{\{\vec{x} = \vec{x}_0\}} \right]$$

thus

$$\begin{aligned} \vec{x} = \vec{x}_0 - \vec{\Delta}_r &\Rightarrow \text{drift of } f \text{ at } \vec{x} = h_r(\vec{x}) = h_r(\vec{x}_0 - \vec{\Delta}_r) \\ \vec{x} = \vec{x}_0 &\Rightarrow \text{drift of } f \text{ at } \vec{x} = - \sum_r h_r(\vec{x}_0) \\ \text{else} &\quad \text{drift of } f \text{ at } \vec{x} = 0 \end{aligned}$$

Apply the drift equation and obtain the theorem.

□

---

**EXAMPLE: IMMIGRATION-DEATH PROCESS.** Let  $p_x = \mathbb{P}\{X(t) = x\}$  for  $x = 0, 1, 2, \dots$ ; we have the set of differential equations:

$$\frac{dp_x}{dt} = \lambda p_{x-1} + (x+1)\mu p_{x+1} - (\lambda + x\mu)p_x \text{ for } x = 1, 2, \dots \quad (1.35)$$

$$\frac{dp_0}{dt} = \mu p_1 - \lambda p_0 \quad (1.36)$$


---

**QUESTION 1.4.2.** *If you set the derivative equal to 0 in Equation (1.35) and Equation (1.36), which equations do you obtain ?*

The master equation is mainly theoretical. Its solution is possible, even numerically, only for very small state spaces.

## 1.5 DETERMINISTIC REACTION MODELS

### 1.5.1 APPROXIMATION BY ORDINARY DIFFERENTIAL EQUATION

We are interested in this section in systems where the dynamics is large, probably because they start from initial conditions that are very far from the long run average (see Figure 1.1 for some examples). Such systems can be approximated by deterministic equations. Here again, the starting point is the drift equation. Apply the drift equation to the functions  $f(\vec{X}) := X_s$ . We obtain:

$$\frac{d\bar{x}_s}{dt} = \sum_r \mathbb{E} \left( h_r(\vec{X}(t)) \right) \Delta_{r,s} \quad (1.37)$$

where  $\bar{x}_s = \mathbb{E}(X_s)$  (recall that  $\Delta_{r,s}$  is the effect of the  $r$ th reaction on  $X_s$ ). Assume that we can neglect the variability of  $X_s(t)$  around its mean value  $\bar{x}_s$ ; then one can write the approximation:

$$\mathbb{E} \left( h_r(\vec{X}(t)) \right) \approx h_r \left( \mathbb{E}(\vec{X}(t)) \right) \quad (1.38)$$

**DEFINITION 1.5.1 (Associated ODE).** *Consider a stochastic reaction model with state space  $\mathcal{S} = \mathbb{N}^S$ . The **associated ordinary differential equation (ODE)** is the differential equation system:*

$$\frac{d\vec{x}}{dt} = \sum_r h_r(\vec{x}) \vec{\Delta}_r \quad (1.39)$$

where  $\vec{x}(t)$  is a vectorial function of time  $t$ , with values in  $\mathbb{R}^S$

Thus, if the approximation in Equation (1.38) is valid, the vector of means  $(\bar{x}_1, \dots, \bar{x}_S)$  satisfies the associated ODE. The associated ODE is similar to the drift equation, however, there are some differences:

- the quantities  $x_s(t)$  in Equation (1.39) are real numbers, not integers
- the drift equation contains expectations, the ODE does not.



---

EXAMPLE: **IMMIGRATION-DEATH PROCESS**. The vector of mean here is a scalar  $x(t)$  and the ODE is:

$$\frac{dx}{dt} = \lambda - \mu x \quad (1.40)$$

The mean of the process  $\bar{x}(t)$  satisfies exactly this ODE, as we saw in Example 1.8 on page 17. This is because all rates are linear in the state vector, in which case Equation (1.38) is exact.

---



---

EXAMPLE: **IMMUNE REACTION**. The vector of mean here is  $(\bar{T}(t), \bar{I}(t), \bar{E}(t))$ . The ODE is here a set of three simultaneous equations:

$$\frac{d\bar{T}}{dt} = \sigma - \beta\bar{T}\bar{I} - \delta_T\bar{T} \quad (1.41)$$

$$\frac{d\bar{I}}{dt} = \beta\bar{T}\bar{I} - k\bar{I}\bar{E} - \delta_I\bar{I} \quad (1.42)$$

$$\frac{d\bar{E}}{dt} = \alpha\bar{I}\bar{E} - \delta_E\bar{E} \quad (1.43)$$

Here the equation is only approximately true for the vector of means. A true equation for  $\bar{T}$  is

$$\begin{aligned} \frac{d\bar{T}(t)}{dt} &= \sigma - \beta\mathbb{E}(T(t)I(t)) - \delta_T\bar{T}(t) \\ &= \sigma - \beta(\bar{T}\bar{I} + \text{cov}(T(t), I(t))) - \delta_T\bar{T}(t) \end{aligned}$$

where we used the identity  $\mathbb{E}(TI) = \mathbb{E}(T)\mathbb{E}(I) + \text{cov}(T, I)$ . If the variability of  $T(t)$  and  $I(t)$  is small, then the standard deviations  $\sigma_{T(t)}$  and  $\sigma_{I(t)}$  are small compared to the means  $\bar{T}(t)$  and  $\bar{I}(t)$ , thus  $|\text{cov}(T(t), I(t))| \leq \sigma_{T(t)}\sigma_{I(t)}$  is also small compared to  $\bar{T}(t)$  and  $\bar{I}(t)$ .

The approximation is also valid if the variability is high but if we can assume that  $T(t)$  and  $I(t)$  are independent.

---

It can be shown that the ODE becomes exact if we scale the system such that the reaction rates are large and the effects are small, i.e. the system implies a large number of small changes. More precisely, if we replace  $\vec{\Delta}_r$  by  $\epsilon\vec{\Delta}_r$  and  $h_r(\vec{x})$  by  $\frac{1}{\epsilon}h_r(\vec{x})$ , then, as  $\epsilon$  goes to 0, the vector of means of the stochastic systems converges, in some sense, to a solution of the ODE.

---

EXAMPLE 1.9: **REGULATED POPULATION**. A population of cells is generated at a constant rate  $\lambda^2$  and subject to homeostatic regulation with rate  $\gamma^2$ . Let  $\bar{x}(t)$  be the mean population. The associated ODE is

$$\frac{dx}{dt} = \lambda^2 - \gamma^2 x^2 \quad (1.44)$$

which, using a symbolic computation package, gives

$$x(t) = \frac{\lambda \frac{1 + \frac{-\lambda + \gamma x_0}{\lambda + \gamma x_0} e^{-2\lambda\gamma t}}{\gamma \frac{1 - \frac{-\lambda + \gamma x_0}{\lambda + \gamma x_0} e^{-2\lambda\gamma t}}}{\quad} \quad (1.45)$$

where  $x_0$  is the initial condition. The long run limit is

$$x^* = \lim_{t \rightarrow +\infty} x(t) = \frac{\lambda}{\gamma} \quad (1.46)$$

Now let us compare to the mean of the long run distribution. The long run distribution of state  $\pi(x)$  satisfies the balance equation, for  $x = 0, 1, 2, \dots$ :

$$\begin{aligned} \pi(x)(\lambda^2 + x^2\gamma^2) &= \pi(x-1)\lambda^2 + \pi(x+1)\gamma^2(x+1)^2 \\ \pi(0)(\lambda^2 + x^2\gamma^2) &= \pi(1)\gamma^2 \end{aligned}$$

This can be solved iteratively and one finds

$$\pi(x) = K \frac{\lambda^{2x}}{\gamma^{2x}(x!)^2} \quad (1.47)$$

where  $K$  is the normalizing constant, with

$$K^{-1} = \sum_{x=0}^{+\infty} \frac{\lambda^{2x}}{\gamma^{2x}(x!)^2} = I_0\left(2\frac{\lambda}{\gamma}\right)$$

where  $I_0()$  is the modified Bessel function of order 0. The long run mean of the distribution of the population is

$$\begin{aligned} \bar{x}^* &:= \sum_{x \in \mathbb{N}} x\pi(x) = K \sum_{x \in \mathbb{N}} \frac{x\lambda^{2x}}{\gamma^{2x}(x!)^2} = K \frac{\lambda}{\gamma} I_1\left(2\frac{\lambda}{\gamma}\right) \\ &= \frac{\lambda}{\gamma I_0\left(2\frac{\lambda}{\gamma}\right)} I_1\left(2\frac{\lambda}{\gamma}\right) \end{aligned}$$

where we used the fact that  $I_1()$  (modified Bessel function of order 1) is the derivative of  $I_0()$ . The Bessel functions are special functions, which are available in many software tools. In Figure 1.4 we plot the approximation  $x^*$  and the true value  $\bar{x}^*$  against the ratio  $\frac{\lambda}{\gamma}$ . We see that the approximation becomes better for large values: this corresponds to the convergence result mentioned earlier. When  $\frac{\lambda}{\gamma}$  is large, the population size is in average large compared to the increase or decrease due to one reaction, thus the approximation by the ODE is good. We see that even for small average population sizes, the approximation is good.

---

QUESTION 1.5.1. *The exact value is below the approximate. Can you make sense of this ?*

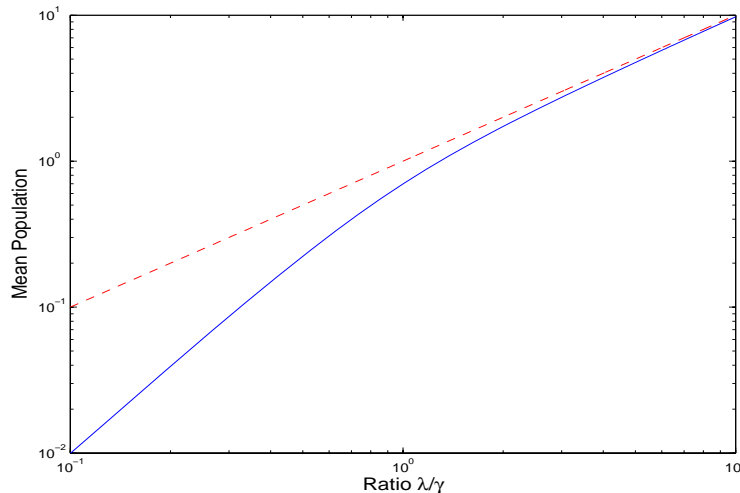


Figure 1.4: Long run average of the number of individuals in the regulated population model of Example 1.9 on page 19: exact value (plain) obtained by solution of the master equation and approximate value (dashed) predicted by the ODE method.

### 1.5.2 STABLE POINTS OF ODE

When the ODE approximation is valid, it gives a much more useful method to study the system. In particular, one can easily obtain information about possible *stable points*, i.e. values towards the system converges when starting from appropriate initial conditions. Stable points are obtained by setting the derivative equal to 0 in the ODE, i.e, these are the points that simultaneously satisfy all equations

$$0 = \sum_r h_r(\vec{x}) \Delta_{r,s} \quad (1.48)$$

for all values of  $s$ .

However, not all points that satisfy this condition (called *equilibrium points*) are stable.

**QUESTION 1.5.2.** *What are the equilibrium points of the associated ODE of the immigration-death model? Which ones are stable points?*

To see whether an equilibrium point is stable, one can use the differential (also called *Jacobian matrix*) of the right-handside of the ODE at this point. This is the matrix  $\left( \left( \frac{\partial f_s}{\partial x_r} \right)_{r,s} \right)$ , where  $f_s(\vec{x})$  is the right-handside in Equation (1.48), and  $\vec{x}$  is the equilibrium point. If all eigenvalues of the matrix have a negative real part, then  $\vec{x}$  is a stable point. More precisely, this condition means that the point  $\vec{x}$  is asymptotically stable, i.e. if we take initial conditions  $\vec{X}(0)$  close enough to  $\vec{x}$ , then  $\vec{X}(t)$  remains in the neighborhood of  $\vec{x}$  (stability) and further, the long-run limit is  $\vec{x}$  (asymptotic stability).

---

**EXAMPLE 1.10: IMMUNE RESPONSE.** The associated ODE is given by Equations 1.41 to 1.43. Steady-state values are obtained by the set of equations

$$\begin{aligned} \sigma - \beta TI - \delta_T T &= 0 \\ \beta TI - kIE - \delta_I I &= 0 \\ \alpha IE - \delta_E E &= 0 \end{aligned}$$

which is equivalent to

$$\begin{aligned}\sigma - \beta T I - \delta_T T &= 0 \\ \beta T - k E - \delta_I &= 0 \quad \text{or} \quad I = 0 \\ \alpha I - \delta_E &= 0 \quad \text{or} \quad E = 0\end{aligned}$$

This gives 4 cases in total, depending which branch is chosen in the second and third equations. One of the four cases has no solution ( $I = 0, \alpha I - \delta_E = 0$ ), which leaves us with 3 possible equilibrium points:

$$\begin{aligned}x_1^* &= \left( \frac{\sigma}{\delta_T}, 0, 0 \right) \\ x_2^* &= \left( \frac{\delta_I}{\beta}, \frac{\sigma}{\delta_I} - \frac{\delta_T}{\beta}, 0 \right) \\ x_3^* &= \left( \frac{\sigma}{\beta \frac{\delta_E}{\alpha} + \delta_T}, \frac{\delta_E}{\alpha}, \left( \frac{\sigma}{\frac{\delta_E}{\alpha} + \frac{\delta_T}{\beta}} - \delta_I \right) \frac{1}{k} \right)\end{aligned}$$

The equilibrium points  $x_2^*$  and  $x_3^*$  exist only if the expressions that define them are non negative, i.e.  $x_2^*$  exists only if  $\frac{\sigma}{\delta_I} \geq \frac{\delta_T}{\beta}$  and i.e.  $x_3^*$  exists only if  $\frac{\sigma}{\frac{\delta_E}{\alpha} + \frac{\delta_T}{\beta}} \geq \delta_I$ .

The Jacobian matrix is

$$J = \begin{bmatrix} -\beta I - \delta_T & -\beta T & 0 \\ \beta I & \beta T - k E - \delta_I & -k I \\ 0 & \alpha E & \alpha I - \delta_E \end{bmatrix}$$

We now take the values of the parameters  $\alpha, \beta, \dots$  as in Figure 1.2. For these values, the three equilibrium points exist. A numerical software tool such as Matlab gives the eigenvalues for the three cases:

$$\begin{aligned}\text{for } \vec{x} = x_1^* : \vec{\lambda} &= (-0.1000, 99.9000, -0.0100) \\ \text{for } \vec{x} = x_2^* : \vec{\lambda} &= (-99.9000, -0.1000, 0.9890) \\ \text{for } \vec{x} = x_3^* : \vec{\lambda} &= (-0.5446 + 2.9787i, -0.5446 - 2.9787i, -0.0108)\end{aligned}$$

It follows that only  $x_3^*$  is a stable point. It is shown by dotted lines and circles in the figures. Figure 1.5 shows a numerical solution of the ODE for these values of the parameters. We see that there is convergence to  $x_3^*$ , but the convergence of  $E(t)$  is very slow.

---

QUESTION 1.5.3. Compare Figure 1.2 and Figure 1.5. Can you explain the difference ?

### 1.5.3 NUMERICAL SOLUTION OF ODE

In some (rare) cases it is possible to solve the ODE explicitly. In all other cases, one needs to solve it numerically (this is also called a simulation). Simulating the ODE can be done in a simple way using *Euler's method*. The idea is to pretend that the derivative  $\frac{d\vec{x}}{dt}$  in Equation (1.39) is the same as the increase ratio  $\frac{\vec{x}(t+\delta) - \vec{x}(t)}{\delta}$ : then we compute the value of  $\vec{x}(n\delta)$  iteratively for  $n = 1, 2, \dots$

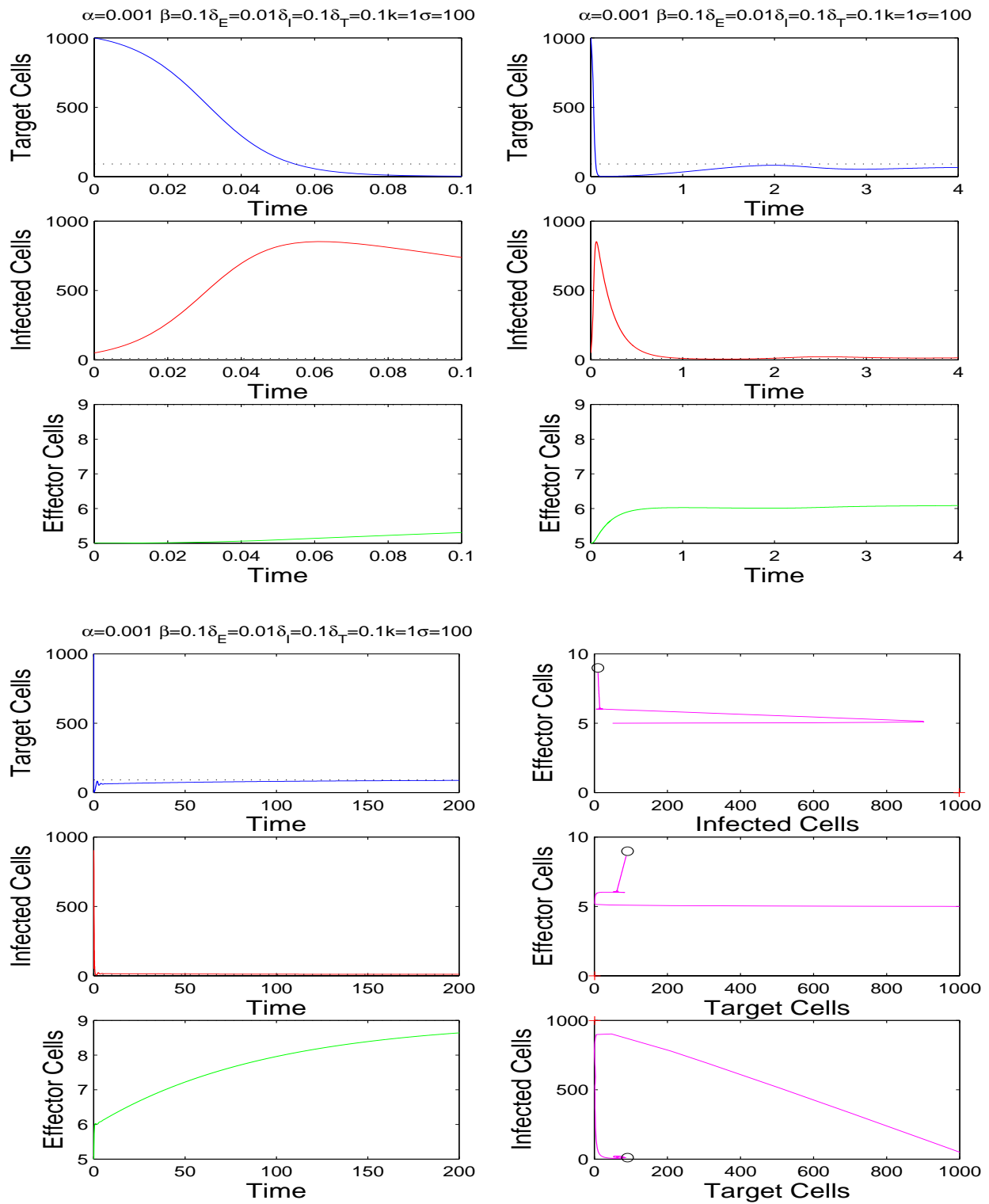


Figure 1.5: Numerical Solution of the associated ODE for the Immune Response model, and the same parameter values as Figure 1.2.

**Algorithm 3** Euler's Method

---

```

1: procedure EULER( $T_{\max}, \vec{x}_0, \delta$ )
                                     ▷  $T_{\max}$ : maximum duration of simulation
                                     ▷  $\vec{x}_0$ : initial state
                                     ▷  $\delta$ : time step
2:    $\vec{x} \leftarrow \vec{x}_0$ 
3:    $t = 0$ 
4:    $n_{\max} = \text{floor}(\frac{T_{\max}}{\delta})$ 
5:   for  $n \leftarrow 1, n_{\max}$  do
6:     for  $r \leftarrow 1, R$  do
7:        $\vec{x} \leftarrow \max\left(\vec{x} + \delta \sum_r h_r(\vec{x}) \Delta_r, \vec{0}\right)$ 
8:     end for
9:     output( $t, \vec{x}$ )
10:  end for
11: end procedure

```

---

Euler's algorithm is simple, but it has to be used with care. If the time step  $\delta$  is not small enough, it may not give a good approximation. A simple check is to decrease the time step until the solution does not change. Some software packages are more efficient as they adjust the time step automatically. Further, there are better approximations than to replace the derivative by the increase ratio (for example the Runge-Kutta method).

## 1.6 HYBRID METHODS

### 1.6.1 HYBRID REACTION MODEL

Consider a stochastic reaction model where some reactions (the *fast reactions*) satisfy the conditions for the associate ODE to be accurate, i.e., the rates are high and the effects are small, but not all. Then it is possible to simulate the fast reactions using the ODE, and the other reactions using a stochastic algorithm.

---

**EXAMPLE: IMMUNE REACTION.** Figure 1.2 shows that the population of effectors with these parameter values varies slowly, unlike the populations of target and infected cells. Also, the rates of reactions 4 and 7 are small compared to the others. Thus one could simulate all reactions except 4 and 7 with the ODE.

It follows that  $T(t)$  and  $I(t)$  vary due to both deterministic and stochastic reactions. In contrast,  $E(t)$  is updated only when a stochastic reaction occurs.

---

Simulation of a hybrid reaction model works as follows.

- When a stochastic reaction  $r$  fires, say at time  $T_1$ , update all variables by

$$X_s(T_1) := X_s(T_1^-) + \Delta_{r,s} \quad (1.49)$$

for all  $s$ , where  $X_s(T_1^-)$  is the state of species  $s$  just before  $T_1$ .

- Let  $T_2$  be the time of occurrence of the first stochastic reaction after  $T_1$  (this may not be the same reaction as  $r$ , which fired at  $T_1$ ). Between  $T_1$  and  $T_2$ , update all variables by solving the ODEs

$$\frac{dX_s}{dt} = h_r(X_s)\Delta_{r,s} \quad (1.50)$$

for all  $s$ , for  $t \in [T_1, T_2]$  and with initial value  $\vec{X}(T_1)$  given by Equation (1.49).

The problem is how to draw the time  $T_2$  once the transition at  $T_1$  has fired, i.e. draw the time delay until the occurrence of any next stochastic reaction. It is not possible to simply use Gillespie's direct method, as the rates of the stochastic reaction may involve the fast reactions. This is the case in the example above for reaction 4, which is stochastic; its rate,  $\alpha IE$ , varies continuously because  $I(t)$  is updated by the ODE.

A solution to this problem is as follows. Intuitively, the probability  $h_r(\vec{X})$  that the stochastic reaction  $r$  fires in the next  $dt$  seconds is  $h_r(\vec{X}(t))$ . During the time interval until next occurrence of reaction  $r$ , we can view the rate as a given time varying function  $\lambda(t)$ . The problem now becomes: sample the time at which the next transition will occur, knowing that the rate of probability that it fires in the next  $dt$  seconds, given that it has not yet fired, is  $\lambda(t)$ . One solution to this problem is as follows: draw a random variable  $Y$  according to the exponential distribution with rate 1. Set the time  $T$  by the condition

$$\int_t^{t+T} \lambda(s)ds = Y \quad (1.51)$$

and the next transition time is  $T_2 = T_1 + T$ .

One can check that if the rate  $\lambda$  is constant, then  $T = \frac{Y}{\lambda}$ . Otherwise, one needs to solve this equation numerically, by approximating the integral. In Algorithm 4, the approximation is by step functions.

An intuitive description of Equation (1.51) is in terms of *credits*. One draws a credit for reaction  $r$  from the exponential distribution with rate 1. Then the credit is burnt at rate  $\lambda(t)$ . When the credit reaches 0, the reaction occurs. This is the basis of the hybrid simulation method presented in Algorithm 4.

**Algorithm 4** gives a possible simulation method for the hybrid model. The algorithm runs up to time  $t_{\max}$  approximately. It can slightly overshoot the maximum simulation time  $t_{\max}$  – this can be fixed by changing the exit conditions around line 13.

Line 10 implements Equation (1.49). It differs slightly, however. First, due to the finiteness of the time step  $\delta$ , it is possible that more than one reactions fire in the same time step (which is theoretically impossible for the Markov process). Second, it follows that the update rules are inconsistent, this is why the max term is used to avoid impossible states.

See Figure 1.6 for sample simulation runs using this algorithm.

**Note** The Gillespie's *next reaction* algorithm, also called *Gibson-Bruck's* algorithm, is similar to the hybrid algorithm we presented here, but applies to the pure stochastic reaction case [?].

**Algorithm 4** Hybrid Algorithm

---

```

1: procedure HYBRID( $T_{\max}, \vec{x}_0, \delta$ )
     $\triangleright T_{\max}$ : maximum duration of simulation
     $\triangleright \vec{x}_0$ : initial state
     $\triangleright \delta$ : time step

2:   StochasticReactions, DeterministicReactions: Sets of reactions
3:    $t = 0; \vec{x} = \vec{x}_0$ 
4:   for all  $r \in$  StochasticReactions do
5:     draw  $\text{credit}(r) \sim \text{Exp}(1)$ 
6:   end for

7:   loop
8:     nextReaction( $t_i$ , FiredReactions,  $\vec{x}_i$ , credit)
9:      $t \leftarrow t + t_i$ 
10:     $\vec{x} \leftarrow \max\{\vec{x}_i + \sum_{r \in \text{FiredReactions}} \vec{\Delta}_r, \vec{0}\}$ 
11:    output( $t, \vec{x}$ )
12:    if  $t > t_{\max}$  then
13:      break
14:    end if
15:    for  $r \in$  FiredReactions do
16:      draw  $\text{credit}(r) \sim \text{Exp}(1)$ 
17:    end for
18:  end loop
19: end procedure

20: function NEXTREACTION( $t_i$ , FiredReactions,  $\vec{x}_i$ , credit)
     $\triangleright$  Advances the simulated time until a stochastic reaction fires
     $\triangleright$  FiredReactions: set of reactions fired
     $\triangleright t_i$ : incremental time until next stochastic reaction
     $\triangleright \vec{x}_i$ : input: initial state; output: final state just before stochastic reactions
     $\triangleright$  credit: input: initial credits; output: credits when reaction occurs
     $\triangleright$  credit: output: credits when reaction occurs

21:    $t_i = 0; \text{FiredReactions} \leftarrow \emptyset$ 
22:   for  $n = 1, n_{\max}$  do
23:      $t_i \leftarrow t_i + \delta$ 
24:      $\vec{x}_i \leftarrow \max\{\vec{x}_i + \delta \sum_{r \in \text{DeterministicReactions}} \vec{\Delta}_r h_r(\vec{x}_i), \vec{0}\}$ 
25:     for all  $r \in$  StochasticReactions do
26:        $\text{credit}(r) \leftarrow \text{credit}(r) - h_r(\vec{x}_i)\delta$ 
27:       if  $\text{credit}(r) \leq 0$  then
28:         FiredReactions  $\leftarrow$  FiredReactions  $\cup \{r\}$ 
29:       end if
30:     end for
31:     if FiredReactions =  $\emptyset$  then
32:       output( $t, \vec{x}$ )
33:     else
34:       break
35:     end if
36:   end for
37: end function

```

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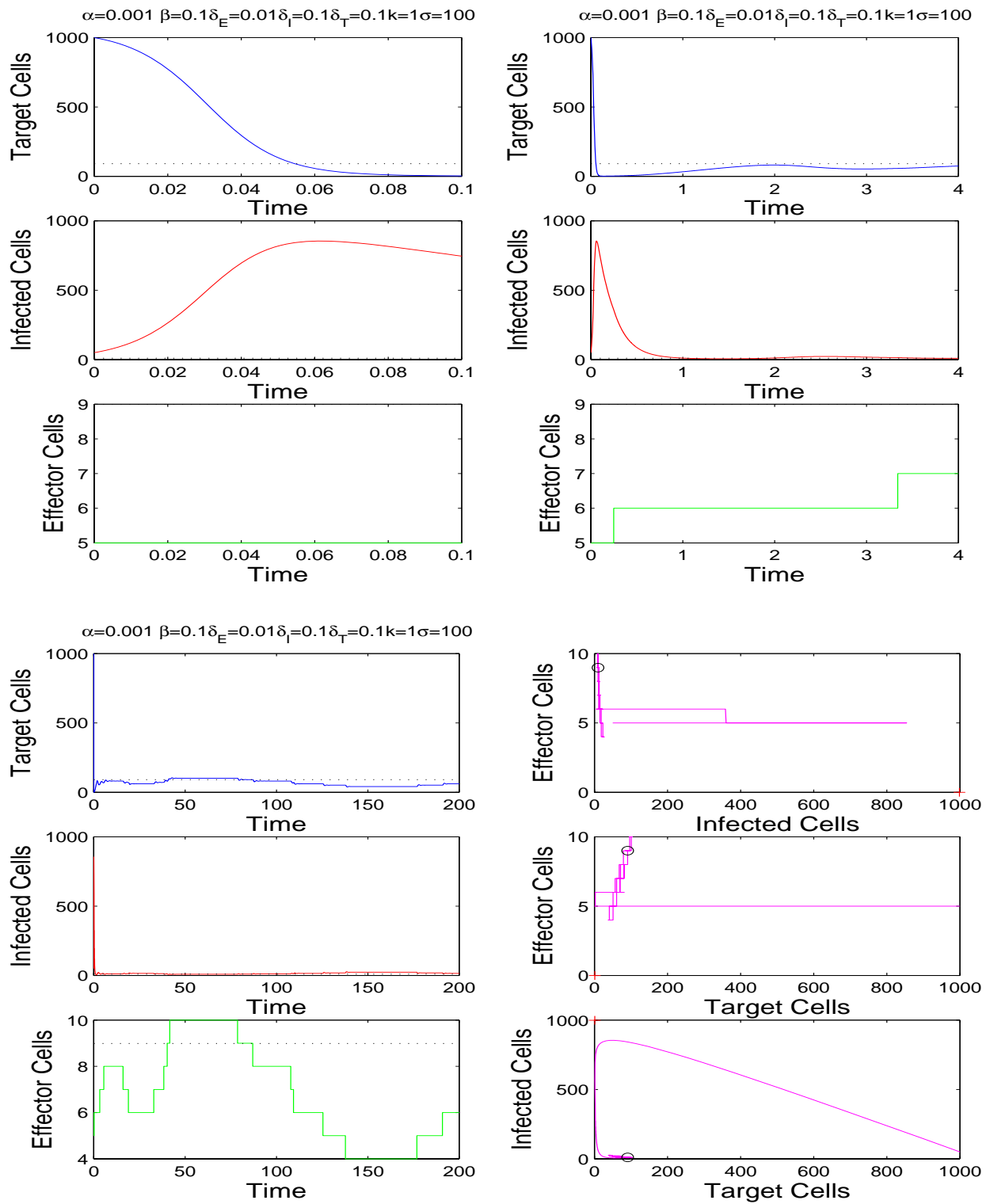


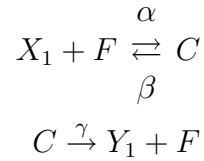
Figure 1.6: Hybrid simulation of Immune Response model, where the reactions that control the evolution of  $I(t)$  are stochastic, and all others are deterministic. Same parameter values as Figure 1.2.

### 1.6.2 HYBRID METHOD WITH QUASI-STEADY STATE

In the previous section we saw how to simplify the study of a stochastic reaction model by replacing the fast reactions by their associated ODE. In this section we go one step further.

Assume the fast reactions converge quickly to some equilibrium. The idea is now to do as if the fast reaction would immediately get into equilibrium. This is called the *quasi-steady state* approximation. We explain it on one important example.

**Explaining the Michaelis-Menten Reaction Model.** This model was described in Section 1.2.4. We can explain Equation (1.24) if we assume it to be the result of the following network of reactions:



where  $F$  is the facilitator and  $C$  is the complex made of  $X_1$  and  $C$ .

The Michaelis-Menten reaction model occurs if we can assume that the reaction rates  $\alpha$  and  $\beta$  are large compared to  $\gamma$  and the concentration of the facilitator  $F$  is small compared to  $X_1$ . We can thus consider the first two reactions as deterministic. Between two firings  $T_1$  and  $T_2$  of the third reaction, we have

$$\begin{aligned} \frac{dX_1}{dt} &= -\alpha X_1 F + \beta C \\ \frac{dF}{dt} &= -\alpha X_1 F + \beta C \\ \frac{dC}{dt} &= \alpha X_1 F - \beta C \end{aligned} \tag{1.52}$$

Now we make the steady-state assumption for the concentration of the complex  $C$ . This means that soon after  $T_1$ ,  $C$  has reached its equilibrium value. This value is given by setting Equation (1.52) to 0, thus

$$\alpha X_1 F = \beta C \tag{1.53}$$

Now, note that the conservation law for this set of reactions gives

$$F + C = f_0 \tag{1.54}$$

where  $f_0$  is the total amount of facilitator units (free or engaged in complexes).

Using Equations (1.53) and (1.54) we can solve for  $C$  and obtain

$$C = \frac{\alpha X_1 f_0}{\beta + \alpha X_1} \tag{1.55}$$

Thus, soon after  $T_1$ , the rate of the stochastic reaction is

$$\gamma C = \frac{\gamma X_1 f_0}{\frac{\beta}{\alpha} + X_1} \tag{1.56}$$

Now, since the amount of facilitator  $f_0$  is assumed to be small, we can equate  $X_1$  with the number of units of species 1 present in the system described by Equation (1.24). This explains the form of

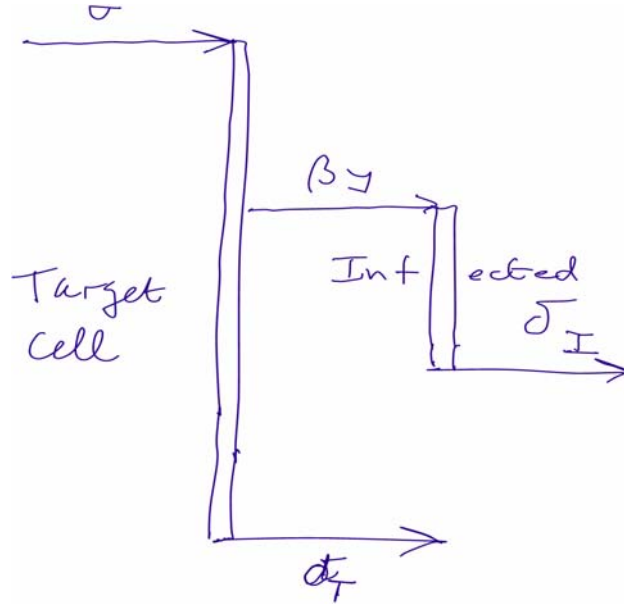


Figure 1.7: Basic reproductive ratio for Immune Response Model.

the reaction rate in Equation (1.25) by letting  $x_1^* = \frac{\beta}{\alpha}$  and  $\lambda = \gamma f_0$ . The other cases in Section 1.2.4 are explained similarly.

This method can be generalized to many other types of reactions [1].

## 1.7 REPRODUCTIVE NUMBER

For the immune response model of Section 1.2.2, the *reproductive number* is the ratio  $R_0 = \frac{\sigma\beta}{\delta_T\delta_I}$ . It is necessary that  $R_0 > 1$  for the infection to be sustainable. To see why, consider Figure 1.7.

Assume some period of time during which the number of infected cells  $I(t)$  can be considered approximately constant. One target cell creates 1 infected cell with probability  $\frac{\beta y}{\beta y + \delta_T}$ . The rate of creation of infected cells is thus

$$\lambda = \sigma \frac{\beta y}{\beta y + \delta_T} \quad (1.57)$$

One infected cell lives in average  $\frac{1}{\delta_I}$ . By Little's law, the quasi-stationary number of infected cells is:

$$y = \lambda \frac{1}{\delta_I} = \sigma \frac{\beta y}{\beta y + \delta_T} \frac{1}{\delta_I} \quad (1.58)$$

from where we derive

$$\sigma\beta = \delta_I\beta y + \delta_T\delta_I \quad (1.59)$$

for  $y > 0$  to be possible we need  $\sigma\beta > \delta_T\delta_I$ .

## 1.8 EXERCISES

### 1.8.1 REVIEW QUESTIONS

QUESTION 1.8.1. *What does the convergence of a stochastic reaction model mean ? Compare this to the convergence of a deterministic reaction model.*

QUESTION 1.8.2. *Give a representation of the Immigration-Death process as a stochastic reaction network.*

QUESTION 1.8.3. *Which of the following simulation methods of a stochastic reaction network provide outputs that may differ from one run to the other:*

1. *Gillespie's direct method*
2. *Solution of the associated ODE*
3. *The hybrid method.*

QUESTION 1.8.4. *The proliferation of naive T cells is controlled by homeostasis.*

1. *Give a stochastic reaction model for the population of naive T-cells.*
2. *Write the associated ODE.*

QUESTION 1.8.5. *Consider the immune response model of Section 1.2.2. We want to add into the model the population of virus particles  $V(t)$ . Write the corresponding reaction model*

### 1.8.2 PROBLEMS

EXERCISE 1.1. *Consider the immune response model in Section 1.2.2. Use the same values of the parameters as in the figure.*

1. *Implement a simulator using Gillespie's direct method. You can use matlab or any programming environment that you are comfortable with.*
2. *Run the simulator for  $t \in [0, 1]$  and  $t \in [0, 40]$ . Take as initial conditions  $T(0) = 1000$ ,  $I(0) = 50$  and  $E(0) \in \{1, 5, 9, 50\}$ . What qualitative statements can you make on the impact of  $E(0)$  ?*

EXERCISE 1.2. *Consider again the immune response model in Section 1.2.2. Use the same values of the parameters as in the figure.*

1. *Implement a simulator using the ODE method and a numerical solution of it. Verify that you can reproduce the results of Section 1.5.*
2. *Run the simulator for  $t \in [0, 1]$ ,  $t \in [0, 40]$  and  $t \in [0, 400]$ . Take as initial conditions  $T(0) = 1000$ ,  $I(0) = 50$  and  $E(0) \in \{1, 5, 9, 50\}$ . Compare to the results of the previous simulator (using Gillespie's Direct method). Interpret the differences.*

EXERCISE 1.3. *Consider again the immune response model in Section 1.2.2. Use the same values of the parameters as in the figure.*

1. Implement a hybrid method where reactions 4 and 7 are stochastic, and the others are deterministic. Make several runs and compare the different simulation methods with each other.

EXERCISE 1.4. Consider the immigration-death model.

1. Write the drift equation for  $f(x) = x^2$ .
2. Let  $v(t) := \text{var}(X(t))$ . Write an ODE for  $(\bar{x}, v)$ .
3. Solve this equation for initial conditions  $v(0) = 0, \bar{x}(0) = x_0$ .
4. What is the long run value of  $v(t)$ ? Compare with the long run distribution of  $X(t)$

EXERCISE 1.5. 1. Redo the analysis of Example 1.10 on page 21 assuming now we start with initial condition  $I(0) = 0$ .

2. Redo the analysis of Example 1.10 on page 21 assuming now we start with initial condition  $E(0) = 0$ .



# Bibliography

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# CHAPTER 2

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## SOLUTIONS

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**0.0.1 (P. 2).** Where is the answer to an inline question ?

**ANSWER.** In a chapter at the end.

**1.1.1 (P. 2).** Show this

**ANSWER.** For an exponential random variable  $S$  with parameter  $\mu$  we have  $\mathbb{P}\{S \leq t\} = 1 - e^{-\mu t}$ . The half time is the value of  $t$  such that  $\mathbb{P}\{S \leq t\} = 0.5$  from where we derive  $t = \frac{\ln(2)}{\mu}$ .

**1.1.2 (P. 3).** Modify Example 1.1 on page 2 and assume that the sojourn time is constant instead of exponentially distributed. Is  $X(t)$  still a Markov process ?

**ANSWER.** No. In order to simulate the process, we need to have some additional information: the residual sojourn time for each individual present in the system. The process should thus be described as a variable length list:  $X(t) = [R_1(t), \dots, R_n(t)]$  where  $R_j(t) \geq 0$ .

**1.1.3 (P. 4).** Give an approximation of  $(e^{tA})_{i,j}$  valid for small values of  $t$ . (Hint: use Equation (1.1) and Equation (1.3))

**ANSWER.** For  $i \neq j$ :  $(e^{tA})_{i,j} = A_{i,j}t + o(t)$  and  $(e^{tA})_{i,i} = 1 + A_{i,i}t + o(t)$ .

**1.2.1 (P. 7).** Show how an arbitrary Markov process on a finite space can be described as a stochastic reaction model.

**ANSWER.** Consider one reaction for every couple  $(\vec{x}_0, \vec{y}_0) \in \mathcal{S}$ . The rate of reaction  $r = (\vec{x}_0, \vec{y}_0)$  is  $h_r(\vec{x}) = 0$  for  $\vec{x} \neq \vec{x}_0$  and  $h_r(\vec{x}_0) = A_{\vec{x}_0, \vec{y}_0}$ . The effect is  $\Delta_r = \vec{y}_0 - \vec{x}_0$ .

**1.2.2 (P. 8).** Comment on the variability of the  $X(t)$  from one run to the other.

**ANSWER.** The runs are all different, but show a common deterministic behaviour. The behaviour is very deterministic when the initial condition is far from the equilibrium. It looks relatively more random when the equilibrium is reached.

**1.2.3 (P. 11).** Does this reaction network describe exactly the same Markov process as the stochastic reaction model in Section 1.2.2 ?

**ANSWER.** Yes. You can choose the representation you prefer.

**1.4.1 (P. 17).** Is  $X(t)$  an integer?  $\bar{x}(t)$ ?

**ANSWER.** Yes; no.

**1.4.2 (P. 18).** If you set the derivative equal to 0 in Equation (1.35) and Equation (1.36), which equations do you obtain?

**ANSWER.** The balance equations Equation (1.8) and Equation (1.9).

**1.5.1 (P. 20).** The exact value is below the approximate. Can you make sense of this?

**ANSWER.** The exact drift equation gives

$$\frac{d\bar{x}}{dt} = \lambda^2 - \gamma^2(\bar{x}^2 + \sigma_x^2(t))$$

where  $\sigma_x^2(t) = \text{var}(X(t))$ . At the limit  $\frac{d\bar{x}}{dt} = 0$  and thus

$$(\bar{x}^*)^2 = \frac{\lambda^2}{\gamma^2} - \sigma_x^2 = (x^*)^2 - \sigma_x^2$$

where  $\sigma_x^2$  is the variance of the limiting distribution. Thus  $(\bar{x}^*)^2 < (x^*)^2$ .

**1.5.2 (P. 21).** What are the equilibrium points of the associated ODE of the immigration-death model? Which ones are stable points?

**ANSWER.**  $\lambda - x\mu = 0$  gives one single equilibrium point  $x = \frac{\lambda}{\mu}$ . The derivative is  $-\mu$ , which has a negative real part, thus it is a stable point. We can see on Equation (1.33) that it is the limit of any trajectory.

**1.5.3 (P. 22).** Compare Figure 1.2 and Figure 1.5. Can you explain the difference?

**ANSWER.** The simulation escapes infection as, sooner or later, the stochastic reaction model has  $I(t) = 0$ . In contrast, in the ODE, which uses real numbers, the value of  $I(t)$  may approach 0, but is never exactly 0. As long as the stochastic reaction simulation does not get into  $I(t) = 0$ , it coincides almost with the ODE; after that it does not.

**1.8.1 (P. 30).** What does the convergence of a stochastic reaction model mean? Compare this to the convergence of a deterministic reaction model.

**ANSWER.** The convergence of a stochastic reaction model means that the distribution of state has a limiting value. It does not mean that the state itself converges to a limiting value. In contrast, this is what is meant by convergence of a deterministic reaction model.

**1.8.2 (P. 30).** Give a representation of the Immigration-Death process as a stochastic reaction network.

**ANSWER.**  $S = 1$  species and  $R = 2$  reactions.



**1.8.3 (P. 30).** Which of the following simulation methods of a stochastic reaction network provide outputs that may differ from one run to the other:

1. Gillespie's direct method
2. Solution of the associated ODE
3. The hybrid method.

**ANSWER.**

1. Yes; the output is random, so it differs from one run to the other.
2. In principle no; the output should always be the same. However, be careful to use a valid approximation method (with Euler's algorithm, make sure the time step is small enough).
3. Yes, the output is random, so it differs from one run to the other.

**1.8.4 (P. 30).** The proliferation of naive T cells is controlled by homeostasis.

1. Give a stochastic reaction model for the population of naive T-cells.
2. Write the associated ODE.

**ANSWER.**

1.  $S = 1$  species,  $R = 3$  reactions:
  - Growth: rate  $\lambda X$ , effect:  $X \leftarrow X + 1$
  - Homeostasis: rate  $\gamma X^2$ , effect:  $X \leftarrow X - 1$
  - Death: rate  $\delta X$ , effect:  $X \leftarrow X - 1$
2.  $\frac{dx}{dt} = (\lambda - \delta - \gamma x)x$

**1.8.5 (P. 30).** Consider the immune response model of Section 1.2.2. We want to add into the model the population of virus particles  $V(t)$ . Write the corresponding reaction model

**ANSWER.** We now represent that cells become infected by the virus, not by the  $I$  population. The reactions are

Reaction	Description	Effect	Rate
1	Influx of New Target Cells	$T := T + 1$	$\sigma$
2	Infection	$I := I + 1; T := T - 1$	$\beta TV$
3	Elimination of Infected Cell	$I := I - 1$	$kIE$
4	Proliferation of Effectors	$E := E + 1$	$\alpha IE$
5	Death of target cells	$T := T - 1$	$\delta_T T$
6	Death of infected cells	$I := I - 1$	$\delta_I I$
7	Death of effector cells	$E := E - 1$	$\delta_E E$
8	Proliferation of virus	$V := V + 1$	$\mu I$
9	Death of virus	$V := V - 1$	$\delta_V V$

The modifications are the addition of reactions 8 and 9, and the modification of the rate of reaction 2.