

Lecture 9:

Population Dynamics

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The main purpose of this Lecture is to formulate model dynamical systems which are useful in a biomedical framework and which serve as examples for the later general discussion of dynamical systems.

One consequence of Newtonian physics is the view that only the instantaneous state of the system is needed to determine the future behavior of the system. This viewpoint carries over to all systems that can be described by odes or pdes. For such systems the adequate specification of an initial state leads to the full description of the system as it evolves in time.

As underlined by present circumstances in the financial world this is not true for the “laws” governing economics. As we have learned the system’s past history plays a significant role in how an economic process plays out. There is ample evidence that this may also be true for aspects of biological dynamics, i.e., memory of a systems past plays a role in forecasting the behavior of a system. For example a neuron exhibits a dead time before it is able to fire a next spike. More generally the recovery period of biological resources can play a role in the performance of a piece of tissue or some other population of cells.

Markovian Systems

This said the approximation that a system evolves without memory is still valuable in many biological situations. Stated in somewhat different terms we can think of a system as being in any of a finite number of discrete states say x_i . Then at time intervals say Δt , it can undergo a transition to a new state. In the linear framework that we shall consider this can be written as

$$x_i^{(n+1)} = T_{ij}x_j^{(n)} \quad (9.1)$$

where the summation convention is assumed, and n refers to the n^{th} instant, and $n + 1$ the next time of observation. T_{ij} is the transition matrix of probabilities, so that the matrix element T_{ij} informs us of the probability of passing from the j^{th} state to the i^{th} state. Clearly the entries of \mathbf{T} must be non-negative,

$$T_{ij} \geq 0. \quad (9.2)$$

Since the system must be in some state $x_i^{(n)}$ can be taken to be a *probability vector*, i.e.

$$x_i^{(n)} \geq 0 \ \& \ \sum_{i=1}^N x_i^{(n)} = 1, \quad (9.3)$$

and since the j^{th} state must go somewhere

$$\sum_{i=1}^N T_{ij} = 1. \quad (9.4)$$

From this it follows from (9.1) that

$$\sum_{j=1}^N x_j^{(n+1)} = \sum_{j=1}^N x_j^{(n)} = 1. \quad (9.5)$$

A matrix T_{ij} having the properties (9.2) and (9.4) is called a Markov matrix and repeated application of \mathbf{T}^k , is called a Markov chain. (Recall that the flea/anti-flea scenario of Lecture 4 led to a Markov matrix.) If $\mathbf{T}^k \mathbf{x}^o$ approaches equilibrium \mathbf{x}^e then

$$\mathbf{x}^e = \mathbf{T} \mathbf{x}^e. \quad (9.6)$$

\mathbf{x}^e is an eigenvector corresponding to unit eigenvalue, and \mathbf{x}^e might be deemed to be an equilibrium solution. One might hope that \mathbf{T}^k for k large leads to equilibrium but in two dimensions

$$\mathbf{T}_2 = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix} \quad (9.7)$$

which is clearly a Markov matrix shows that no equilibrium exists, and instead the system undergoes a 2-cycle, for any seed \mathbf{x}^o .

Exercise 9.1. Construct \mathbf{T}_n the analog of (9.7) in n -dimensions. Show that its eigenvalues are the n^{th} roots of unity.

If instead of (9.2) we require that \mathbf{T} be positive, $T_{ij} > 0$, then

$$\mathbf{T}^k \mathbf{x}^o \xrightarrow[k \uparrow \infty]{} \mathbf{x}^e, \quad (9.8)$$

which satisfies (9.6), for arbitrary initial \mathbf{x}^o , i.e., the final state is independent of the initial one.

Exercise 9.2. Use **rand**(n) for say $n = 5$ to generate Markov matrices. (Renormalize **rand**(n) to fulfill (9.4). Obtain the eigenvalues and on this basis give a convincing argument for (9.8) to be true.

Master Equation

If we write (9.1) as

$$\mathbf{x}((n+1)\Delta t) = \mathbf{T}\mathbf{x}(n\Delta t) \quad (9.9)$$

and set $n\Delta t = t$ then for Δt small

$$\Delta t \frac{d\mathbf{x}}{dt} = (\mathbf{T} - \mathbf{1})\mathbf{x} \quad (9.10)$$

and if we set

$$\tilde{\mathbf{T}} = (\mathbf{T} - \mathbf{1})/\Delta t \quad (9.11)$$

we obtain

$$\frac{d}{dt}\mathbf{x} = \tilde{\mathbf{T}}\mathbf{x} \quad (9.12)$$

which is called a *master* equation. From (9.4) it follows that

$$\sum_{i=1}^N \tilde{T}_{ij} \equiv 0 \quad (9.13)$$

and alternately diagonal elements are given by

$$\tilde{T}_{ii} = -\sum_{j \neq i} \tilde{T}_{ij}. \quad (9.14)$$

At equilibrium

$$\tilde{\mathbf{T}}\mathbf{x}^e = 0 \quad (9.15)$$

which from (9.10) is the same condition as (9.6).

In subscript notation (9.12) is

$$\frac{d}{dt}x_i = \sum_j \tilde{T}_{ij}x_j \quad (9.16)$$

Since each column of $\tilde{\mathbf{T}}$ sums to zero

$$\sum_k \tilde{T}_{ki}x_i = 0 \quad (9.17)$$

and if this is subtracted from (9.12) we obtain

$$\frac{d}{dt}x_i = \sum_j (\tilde{T}_{ij}x_j - \tilde{T}_{ji}x_i) = (\mathcal{L}\mathbf{x})_i \quad (9.18)$$

Equation (9.18) is a linear equation with constant coefficients and has the solution

$$\mathbf{x} = e^{\mathcal{L}t} \mathbf{x}^o \quad (9.19)$$

Since \mathbf{x} is a probability vector we must have

$$\sum_i x_i = 1 \quad (9.20)$$

which implies that \mathcal{L} has one zero eigenvalue, which follows from the above discussion of Markov matrices. Based on reversibility considerations from mechanics it is suggested that at true thermodynamic¹ equilibrium we must have

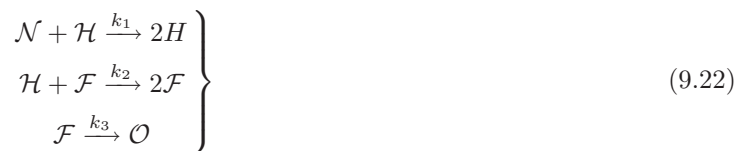
$$\tilde{T}_{ij} x_j = \tilde{T}_{ji} x_i, \quad (9.21)$$

no summation convention. This says that the flux of probability into the i^{th} state from the j^{th} times x_j the probability of being in the j^{th} state is equal to the like flux to the j^{th} state from the i^{th} . This is called the principal of detailed balance and is a condition on the components of $\tilde{\mathbf{T}}$.

Mass Action Equations

A simple model of population dynamics is the predator-prey scenario. For this purpose we assume populations of foxes and hares. Suppose a hare population \mathcal{H} , of number h , and that they are nourished by \mathcal{N} , the natural abundance of the countryside, but are preyed upon by a fox population \mathcal{F} of number f . The foxes die, i.e. they go into the state \mathcal{O} , from natural causes.

This can also be written as



so that k_i are rate constants this gets translated into a system of ordinary differential equations

$$\begin{aligned} \frac{dh}{dt} &= k_1 h - k_2 f h \\ \frac{df}{dt} &= k_2 f h - k_3 f. \end{aligned} \quad (9.23)$$

The rate constants k_j should come from *experiment*.

¹ The thermodynamics argument states that the available energy at constant pressure and temperature, the Gibbs' free energy, must approach its minimum monotonically – which therefore excludes oscillations in the final approach to equilibrium.

In translating (9.22) into (9.23) n the nutrient supply could be introduced as a coefficient of k_1 but in the present instance it is regarded as inexhaustible and is absorbed into k_1 . We can also include the natural death rate for hares which would only slightly offset the value of k_1 . For the present the coefficient 2 in (9.22) is not needed and suggests two hares or two foxes are produced in the normal course of events.

Although the problem is simple it can be formulated somewhat more formally by the graph of Figure 9.1

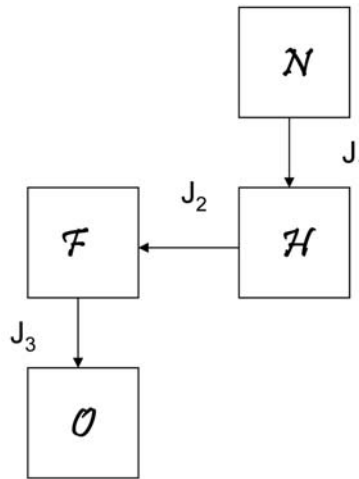


Fig. 9.1: *The flux graph for hare/fox scenario. An arrow indicates a flux out of one box into another box.*

This should read as a flux J_1 into the hare population (the abundance of nourishment leads to procreation) and a flux out J_2 (due to the foxes preying on them). The latter furnishes a flux of population into the fox population, and death by natural causes gives the outflux J_3 to the fox population. The fluxes are

$$\mathbf{J} = \begin{bmatrix} J_1 \\ J_2 \\ J_3 \end{bmatrix} = \begin{bmatrix} k_1 h \\ k_2 f h \\ k_3 f \end{bmatrix} \quad (9.24)$$

in terms of the hare and fox populations h & f , respectively. In such terms the model can be expressed as

$$\frac{d}{dt} \mathbf{c} = \frac{d}{dt} \begin{bmatrix} c_h \\ c_f \end{bmatrix} = \begin{bmatrix} 1 & -1 & 0 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} J_1 \\ J_2 \\ J_3 \end{bmatrix} = \mathbf{S}\mathbf{J}, \quad (9.25)$$

where \mathbf{S} is referred to as the stoichiometric matrix.

In formulating the model we have assumed a homogeneous habitat. Thus h and f refer to actual numbers and c_h & c_f to concentrations, number/area.

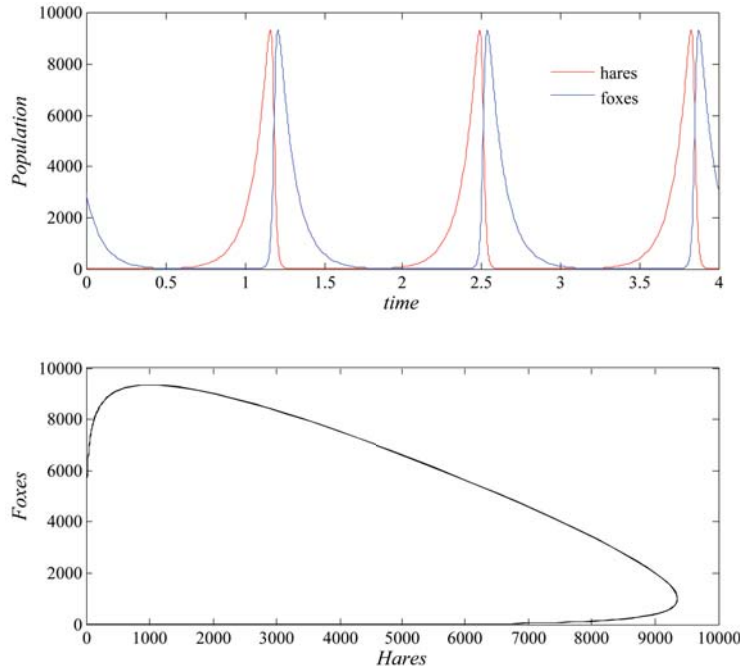


Fig. 9.2: Upper panel shows the result of integrating (9.25) subject to (9.26) & (9.27). The lower panel depicts the phase plane, f versus h .

Additionally, although more subtle is the fact that large populations are being assumed, since we are assuming that the effect of fluctuations is overwhelmed by the large numbers. It is for this reason that a fluctuating system is being described by a deterministic description. Fluctuations become important when the populations are sparse, in which case the formulations take on a different framework, and the results can be significantly different.

In Figure 9.2 (9.25) is simulated for

$$[k_1, k_2, k_3] = [10, .01, 10] \quad (9.26)$$

and initial conditions

$$[c_h^o, c_f^o] = [2, 3000] \quad (9.27)$$

Clearly the populations oscillate with a clearly defined period, with the hare population leading the fox population.

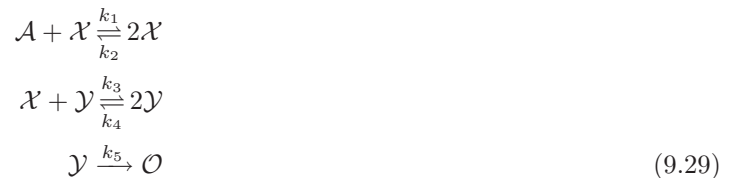
- Exercise 9.3.** (a) Create a program to obtain Figure 9.2
 (b) Experiment with parameters to find interesting situations.
 (c) Solve for equilibrium solutions by imposing

$$\frac{d\mathbf{c}}{dt} = 0, \quad (9.28)$$

and using the neighboring of the equilibria as initial conditions.

Autocatalysis

The above formulation is due to Volterra (1931), and is related to a prior model for autocatalytic chemical reactions proposed by Lotka (1920).



It is called autocatalytic since the reactants \mathcal{X} & \mathcal{Y} are also products. Since chemical reactions can in principle go in both directions the arrows go both ways. We again use lower case letters to speak of concentrations or total numbers in the well-stirred (homogenous) chamber. The usual convention is that the concentration of \mathcal{X} is given by

$$\{\mathcal{X}\} = x (= c_x) \quad (9.30)$$

so that (9.29) leads to

$$\begin{aligned} \frac{da}{dt} &= -k_1 ax + k_2 x^2 \\ \frac{dx}{dt} &= k_1 ax - k_3 xy - k_2 x^2 + k_4 y^2 \\ \frac{dy}{dt} &= k_3 xy - k_4 y^2 - k_5 y, \end{aligned} \quad (9.31)$$

which now indicates why the coefficient 2 appears on the right of (9.29). According to Lotka $k_2 \approx 0$ & $k_4 \approx 0$ and a is large and we get (9.23).

Michaelis-Menton

It has been said that cellular activity is dominated by enzymatic catalysis. The simplest version of this involves a substrate \mathcal{S} , an enzyme \mathcal{E} , a complex \mathcal{C} , and a product \mathcal{P} . This activity is characterized by



so that complex formation is reversible, and some of the complex is producing the desired produce and restoring the remaining enzyme.

The kinetics graphs (9.32) leads to

$$\frac{d}{dt}\mathbf{c} = \frac{d}{dt} \begin{bmatrix} s \\ e \\ c \\ p \end{bmatrix} = \begin{bmatrix} -k_1se + k_2c \\ -k_1se + k_2c + k_3c \\ k_1se - k_2c - k_3c \\ k_3c \end{bmatrix} \quad (9.33)$$

If we define the net fluxes

$$\mathbf{J} = \begin{bmatrix} J_1 \\ J_2 \end{bmatrix} = \begin{bmatrix} -k_2c + k_1se \\ k_3c \end{bmatrix} \quad (9.34)$$

these enter as indicated in Figure 9.3,

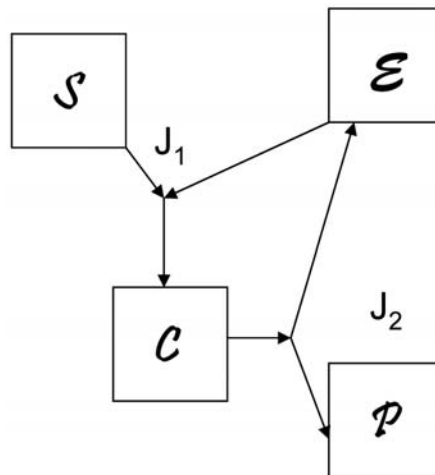


Fig. 9.3: Flux graph for the Michaelis-Menten autocatalytic system (9.33).

and we can then write

$$\frac{d}{dt}\mathbf{c} = \mathbf{S}\mathbf{J} = \begin{bmatrix} -1 & 0 \\ -1 & 1 \\ 1 & -1 \\ 0 & 1 \end{bmatrix} \mathbf{J}. \quad (9.35)$$

In this formatting another feature emerges, viz., that there is a left null space of \mathbf{S} , given by the rows of \mathbf{N} ,

$$\mathbf{N} = \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & -1 & 0 & 1 \end{bmatrix}. \quad (9.36)$$

In Matlab `null` returns the null space of a matrix, and `null(S,'r')` gives rational entries as in equation (9.36).

If these are applied to (9.35) we obtain from the first row of (9.36)

$$\frac{d}{dt}(e + c) = 0 \quad (9.37)$$

and therefore

$$e + c = e^o, \quad (9.38)$$

where e^o is the initial value of e and c is zero initially. From the second row of (9.36) we find

$$s - e + p = s^o - e^o \quad (9.39)$$

Both (9.38) and (9.39) represent conservation laws.

Both (9.38) and (9.39) essentially tell us that matter is being conserved. For example if the process goes to completion we expect $c \xrightarrow[t \uparrow \infty]{} 0$ and therefore e returns to its initial amount. If this is applied to (9.39) it then tells us that

$$p = s^o - s^\infty, \quad (9.40)$$

which should make sense to you. To further use the conserved quantities we might substitute them to reduce the system (9.35) to two equations. Actually the equation for product p is an afterthought in the sense that it can be computed after solving the first three equations of (9.35) which stand alone.

Another possibility for using the conservation laws is to integrate (9.35) and then use (9.38) and (9.39) to verify the accuracy of the calculation.

Exercise 9.4 (Special). (a) Perform a literature search and obtain reasonable values of the rate constants for some real situations.

(b) Solve $\mathbf{S}\mathbf{J} = 0$ of (9.35) to find the equilibria in this instance.

(c) Integrate the system until equilibrium is reached.

(d) Verify the two conservation laws.

In the present example although homogeneity is being assumed, the components are best thought of as concentrations. In the usual terms homogeneity is replaced by the modifier *well-stirred*. The remark about large populations overriding fluctuations is again applicable. When low concentrations occur, which can be the case in a single cell, the model must be reformatted.

Epidemics

The Kermack-McKendrick model of an infectious epidemic divides a population into three parts: susceptibles, \mathcal{S} ; the infected, \mathcal{I} ; those who are removed as a result of immunity or death, \mathcal{R} .



where r is the rate of $\mathcal{S} - \mathcal{I}$ encounters and λ is the removal rate. If we write

$$\{\mathcal{S}\} = c_S; \{\mathcal{I}\} = c_I; \{\mathcal{R}\} = c_R \quad (9.42)$$

then

$$\begin{aligned} \frac{d}{dt}c_S &= -rc_Ic_S \\ \frac{d}{dt}c_I &= rc_Ic_S - \lambda c_I \\ \frac{d}{dt}c_R &= \lambda c_I. \end{aligned} \quad (9.43)$$

This has an immediate conservation law

$$c_S + c_I + c_R = c_S^o + c_I^o \quad (9.44)$$

where zero superscript indicates the initial state ($c_R^o = 0$).

Exercise 9.5 (Optional) (a) Obtain the equilibrium under reasonable hypothesis (e.g., $c_S^\infty \neq 0$). Show

$$f = \frac{c_S^\infty}{c_S^o} = \exp[-\kappa(1 + \frac{c_I^o}{c_S^o} - f)] \quad (9.45)$$

with

$$\kappa = \frac{rc_S^o}{\lambda} \quad (9.46)$$

known as the Kermack number. Note that (9.45) is a relation between three dimensionless ratios.

(b) Use Newton's method (Matlab does not seem to have this and the Appendix to this Lecture furnishes the necessary details.) to generate the surface.

$$f = f(c_I^o/c_S^o, \kappa). \quad (9.47)$$

Only relatively small values of c_I^o/c_S^o are of interest say $c_I^o/c_S^o < .5$ & $0 < \kappa < 2.5$.

Cell Signalling

Mass action applied to cell signalling offers another level of complication and the example that follows is a toy model of cell fate “survival or suicide” based on the study in (Rangamani, P. & Sirovich, L. “Survival and Apoptotic Pathways Initiated by TNF- α : Modeling and Predictions. *Biotechnology and Bioengineering*, 97:1216-1229 (2007)). A cell can undergo programmed death by a process called apoptosis, a non-damaging disposal of a cell², into reusable parts in contrast with necrosis. We will consider a “toy model” of one part of the model in the cited paper.

In simple terms cell signalling is indicated by the arrival and docking of a ligand \mathcal{L} (TNF- α)³ i.e., it attaches to its receptor \mathcal{R} (TNFR1), which lies in the cellular membrane. This forms the complex $\mathcal{C}1$ and represents the first step in the process.



If

$$c_1 = [\mathcal{L}], c_2 = [\mathcal{R}] \ \& \ c_3 = [\mathcal{C}1] \quad (9.49)$$

then

$$\frac{dc_1}{dt} = \underbrace{k_2 c_3 - k_1 c_1 c_2}_{(9.48)} \quad (9.50)$$

$$\frac{dc_2}{dt} = \underbrace{k_2 c_3 - k_1 c_1 c_2}_{(9.48)} + k_3 c_5 \quad (9.51)$$

$$\frac{dc_3}{dt} = \underbrace{-k_2 c_3 + k_1 c_1 c_2}_{(9.48)} + k_5 c_5 - k_4 c_3 c_4 \quad (9.52)$$

where brackets indicate the contributions from (9.48) to the rate of the associated concentrations. Next an inactive form of an enzyme \mathcal{E} (caspase-8) forms a second complex $\mathcal{C}2$



which then disassociates



² For example in development the fingers of a hand are formed by removing the tissue forming the fingers.

³ The association of a biochemical name here and in the following is made in the loosest sense, since it hides the fact that many biochemicals are replaced by a single *alias*

into the active form of \mathcal{E}^* (caspase-3) and also frees up the receptors \mathcal{R} .

Next we define

$$[\mathcal{E}] = c_4, [\mathcal{C}2] = c_5, [\mathcal{E}^*] = c_6 \quad (9.55)$$

which if used in (9.53) yields

$$\frac{d}{dt}c_4 = \underbrace{k_5c_5 - k_4c_3c_4}_{(9.53)} \quad (9.56)$$

and furnishes the additional terms of (9.52).

Then (9.54) yields

$$\frac{d}{dt}c_5 = \underbrace{k_4c_3c_4 - k_5c_5 - k_3c_5}_{(9.54)}, \quad (9.57)$$

$$\frac{d}{dt}c_6 = \underbrace{k_3c_5}_{(9.54)} \quad (9.58)$$

and also furnishes a term in (9.50).

If we define the fluxes

$$\mathbf{J} = \begin{bmatrix} J_1 \\ J_2 \\ J_3 \end{bmatrix} = \begin{bmatrix} -k_2c_3 + k_1c_1c_2 \\ k_3c_5 \\ -k_5c_5 + k_4c_3c_4 \end{bmatrix} \quad (9.59)$$

and

$$\mathbf{c} = [c_1, c_2, \dots, c_6]^\dagger \quad (9.60)$$

then Figure 9.4 indicates how to construct the dynamical system

$$\frac{d\mathbf{c}}{dt} = \mathbf{S}\mathbf{J} \quad (9.61)$$

for this model, where the determination of \mathbf{S} is left as an exercise.

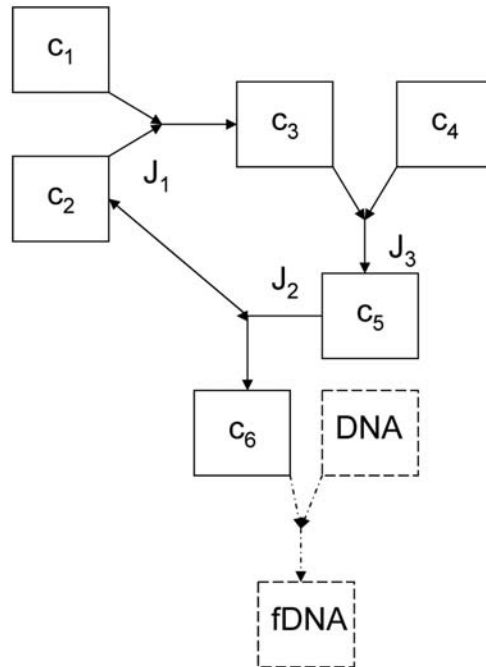


Fig. 9.4: Flux graph for the simple cell signalling model (9.61). The concentrations and reactions involving DNA do not figure in the model.

To complete the picture the active \mathcal{E}^* causes nuclear DNA to fragment, and generates a concentration fragmented DNA, fDNA. This has no back effect on (9.61), which stands alone as a dynamical system, and this is indicated in Figure 9.4.

Exercise 9.6 (Special). (a) Construct the system (9.61) and in particular determine the stoichiometric matrix \mathbf{S} .

(b) Find the left null space of \mathbf{S} .

(c) Find the resulting conserved quantities, and discuss.

(d) Integrate the system (9.61) under the condition that

$$\mathbf{k} = [.175, .002, .185, .003, .1]$$

$$\mathbf{c}^o = [5, 10, 0, 0, 0, 0] \quad (9.62)$$

This toy model only accounts for the apoptotic pathway and hence cell death. In the cited paper a second pathway leading to survival is also included. It does this by the inactivation of \mathcal{E}^* , i.e. a return to \mathcal{E} , by means of nuclear transcription of the inactivating ingredient. Since this involves release of a transcription factor (NF- κ B) which translocates to the nucleus and a subsequent transcription of a protein which binds to

\mathcal{E}^* (caspase-3). All of this takes time and the result is a time delay in the process. This results in a temporal oscillation which has been observed in experiments.

Summary

A number of features of the populational equations that have been developed

$$\frac{d}{dt}\mathbf{c} = \mathbf{F}(\mathbf{c}) \quad (9.63)$$

are unique to this class of equations, and this is worth commenting upon.

(1) The dependent vector is non-negative

$$\mathbf{c} \geq 0. \quad (9.64)$$

A geometrical depiction of this condition is that the trajectory of the dynamical system (9.63) is restricted to the orthant defined by (9.64).

(2) Since the trajectory cannot leave the orthant,

$$\lim_{c_k \rightarrow 0} F_k(\mathbf{c}) \geq 0. \quad (9.65)$$

(3) The direction field \mathbf{F} is at most quadratic, a property shared by equations describing the *top* of classical mechanics, and the equations of fluid mechanics, which describe turbulence.

(4) In the case of chemical kinetics, since matter is conserved conservation equations, which can reduce a system, are generally present and their determination is facilitated by the stoichiometric matrix \mathbf{S} .

(5) The approach to equilibrium for chemical kinetics should respect thermodynamics which requires that the Gibbs energy descends to its minimum (constant temperature & pressure) monotonically.

Appendix: Newton's Method

The object is to find the zeros of

$$f(y) = 0 \quad (9.66)$$

for some general of $f(y)$.

We start by pretending that we know a root $y = y_o$, so that

$$f(y_o) = 0. \quad (9.67)$$

We also assume that y^* is a good guess for y_o . Then

$$0 = f(y + (y_o - y^*)) = f(y^*) + (y_o - y^*) \left. \frac{\partial f(y)}{\partial y} \right|_{y=y^*} \quad (9.68)$$

Therefore

$$y_o = y^* - f(y^*) / \frac{\partial f(y^*)}{\partial y^*} \quad (9.69)$$

or as an algorithm

$$y^{n+1} = y^n - f(x^n) / \frac{\partial f}{\partial y} \Big|_{y=y^n} \quad (9.70)$$

Since (9.68) has an error of $O((y - y^*)^2)$ this procedure converges very quickly. You need a good guess for y^1 .