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Cellular Control Models with Linked Positive and Negative Feedback and Delays. I. The Models

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Basic techniques from biochemical kinetics are used to develop models for a cellular control system with linked positive and negative feedback. The models are represented by a system of nonlinear differential equations with delays. The *lac* operon provides an example of a control system where the transcription of the operon is controlled by induction or positive feedback control and catabolite repression or negative feedback control. These processes are linked through the metabolism of lactose.

1. Introduction

In this series of papers we shall develop and analyze mathematical models of induction linked with repression for prokaryotic cells. These models employ the hypotheses of Jacob & Monod (1961). Goodwin (1963, 1965) proposed mathematical models for induction and repression of the gene. He proposed that epigenetic oscillations in prokaryotic cells may arise from repression of the gene. The Goodwin models of repression have been studied extensively (Griffith, 1968*a*; Walter, 1971; Othmer, 1976; Tyson & Othmer, 1976; and Hastings, Tyson & Webster, 1977). Goodwin also proposed a model for induction. Studies of this mathematical model can be found in Griffith (1968*b*), Othmer (1976) and Tyson & Othmer (1976). The induction models have not been shown to exhibit oscillatory behavior, however, the classical model for induction is the *lac* operon which was shown experimentally by Knorre (1969, 1973) to have at least damped oscillations in asynchronously grown cultures of *E. coli.* Goodwin (1965) suggested that delays and linked genes could be important for oscillatory behavior. The Goodwin models with delays have been studied by Allwright (1977), Hadeler & Tomiak (1977), MacDonald (1977), Banks & Mahaffy (1978*a*), an der Heiden (1979), and Mahaffy (1980). There have been several studies of multiple loops in biochemical control (see Fraser & Tiwari, 1974; Mees & Rapp, 1978; Banks & Mahaffy, 1978*b*). The study below

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is based on the experimental findings concerning the cellular control of the *lac* operon.

When *E. coli* is given a lactose medium as its only carbon source, the cell is induced by a stereoisomer of lactose (allolactose) to produce large quantities of three specific enzymes. One is β-galactoside permease which is involved in the transport of lactose across the cell membrane. Another induced enzyme is β-galactosidase which breaks down lactose into the two simple sugars, glucose and galactose. The third enzyme, β-thiogalactoside acetyl transferase, has not been linked to the metabolism of lactose. This induction process results in a positive feedback to the *lac* operon. However, when the cell has adequate supplies of glucose (independent of the availability of lactose) the *lac* operon does not produce the mRNA necessary to produce large quantities of the enzymes listed above. This process is not completely understood. It appears that glucose affects the lactose metabolism in three ways (Magasanik, 1970). It excludes the inducer from the cells that do not contain a high level of *lac y* gene controlled permease. It also represses β-galactosidase strongly, but transiently. Finally, it works as a catabolite repressor by affecting levels of c-AMP. This last action is weak but permanent during balanced growth. In order for the *lac* operon to be transcribed c-AMP must be available together with CAP (catalytic activator protein). The glucose which is an endproduct of the metabolism of lactose acts as a catabolic repressor by affecting the production of c-AMP and hence indirectly it represses the *lac* operon. The above process is shown in Fig. 1. For more details of the biological processes see Beckwith & Zipser (1970) and Miller & Reznikoff (1978).

In this paper we shall formulate mathematical models based on the biological information given above. To accomplish this the biochemical species given in Fig. 1 will be interrelated by a series of chemical equations which describe the biochemical reactions. These equations will then be transformed into a system of differential equations using some basic principles from chemical kinetics. Several standard ideas from enzyme kinetics and other known information about the system will be used to simplify the models.

2. Biochemical Equations for the Induction–Repression Model

In this section a list of the biochemical reactions is considered for the development of the models with coupled induction and repression. The models will use the biochemical reactions that are known for the *lac* operon as an example of the coupled processes of induction and repression. We note that many of the complexities such as glucose's having three different

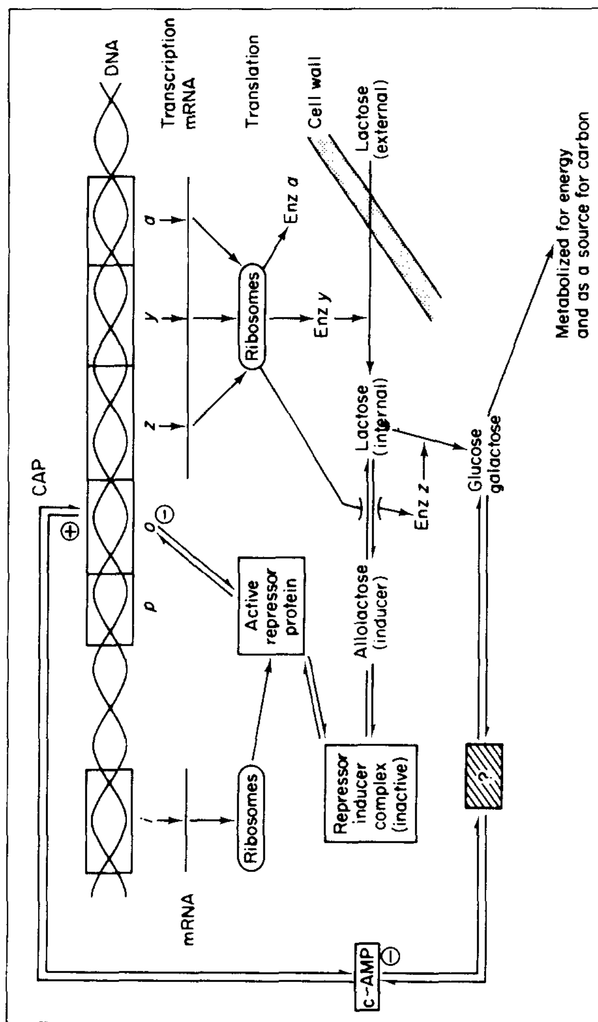


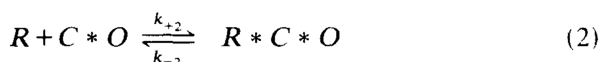
FIG. 1. The *lac* operon. i = regulatory gene; p = promoter gene, o = operator gene; z, y, a = structural genes.

negative feedback roles will not be taken into account. Some of these simplifications may prove to make the behavior of our model deviate from that of the wild type *lac* operon, however, we shall comment on what simplifications have been made and give explanations for our choice of reactions.

To begin the discussion it is noted that CAP and c-AMP are needed to activate the *lac* operon. These chemical species apparently attach to the promoter region splitting the DNA and allowing the initiation complex to form. In the absence of an inducer compound such as allolactose there is a repressor protein bound to the *lac* operon which prevents the gene from transcribing.

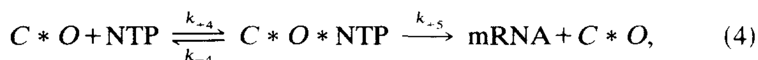
Hence the *lac* operon can be in one of four possible states. Let O represent the free *lac* operon. Let R represent the repressor protein then $R * O$ and $R * C * O$ are the bound inactive complexes formed when the repressor protein is bound to the *lac* operon. Let C represent c-AMP (including the constitutive protein CAP), so $C * O$ is the bound active complex which is ready for the process of transcription. Let NTP represent the nucleoside triphosphate needed to form the initiation complex $C * O * \mathrm{NTP}$. We assume that once the initiation complex is formed the process of transcription proceeds at a steady rate to produce an mRNA. From the above information on the *lac* operon we formulate the following biochemical equations for our induction–repression model:

$$R + O \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} R * O \tag{1}$$



$$R + C * O \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} R * C * O \tag{2}$$

$$C + O \underset{k_{-3}}{\overset{k_{+3}}{\rightleftharpoons}} C * O \tag{3}$$

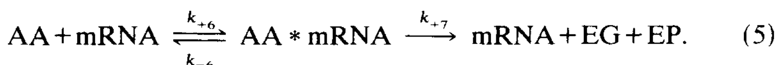


$$C * O + \mathrm{NTP} \underset{k_{-4}}{\overset{k_{+4}}{\rightleftharpoons}} C * O * \mathrm{NTP} \xrightarrow{k_{+5}} \mathrm{mRNA} + C * O, \tag{4}$$

where the ks are the rate constants for the equation determining the rates of formation and decay of the particular chemical species. These equations list the five possible states for the gene of which $C * O$ is the only form allowing for transcription.

The mRNA combines with a ribosome, initiation factors, and an aminoacyl-tRNA to form an initiation complex. After this a specific sequence of amino acids (AA) is added in the process known as translation

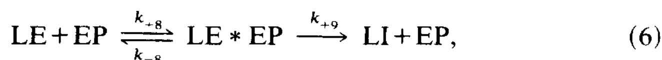
to form the enzymes listed above. Let EP be β-galactoside permease and EG be β-galactosidase. A biochemical equation for the *lac* operon describing this process can be written in the following manner:



$$\mathrm{AA}+\mathrm{mRNA} \underset{k_{-6}}{\overset{k_{+6}}{\rightleftharpoons}} \mathrm{AA}*\mathrm{mRNA} \xrightarrow{k_{+7}} \mathrm{mRNA}+\mathrm{EG}+\mathrm{EP}. \qquad (5)$$

As in the case of transcription, after initiation starts, the process is assumed to go to completion. Experimentally, there is strong evidence indicating that the proteins specified by the structural genes are not produced in equimolar rates (Zabin & Fowler, 1970). Note that both transcription and translation require a significant amount of time to form the completed product, hence these processes should include a delay term in the modeling. The translation in prokaryotic cells begins before transcription is completed, so the delay for transcription should be smaller than the delay for translation.

For the induction–repression model we shall assume that the cell has a constant source of a substance LE which is complexed reversibly to the enzyme EP and irreversibly forms the substance LI which in turn will be changed into the inducer. The basis for our choice is a cell grown on a medium containing lactose as the only source of carbon. β-galactoside permease is involved in the transport of lactose from the exterior of the cell to the interior of the cell against a concentration gradient. The membrane reactions probably involve a complex series of reactions to accomplish this transport (see Kennedy, 1970: Kepes, 1971). These reactions are simplified to the bimolecular reaction between the permease EP and external lactose LE and given by the following chemical reactions:



$$\mathrm{LE}+\mathrm{EP} \underset{k_{-8}}{\overset{k_{+8}}{\rightleftharpoons}} \mathrm{LE}*\mathrm{EP} \xrightarrow{k_{+9}} \mathrm{LI}+\mathrm{EP}, \qquad (6)$$

where LI is the lactose inside the cell. The rate limiting step is the irreversible reaction.

Inside the cell some of the lactose is enzymatically transformed into the natural inducer, allolactose (A). We shall assume that the amount of allolactose is proportional to the amount of LI. This assumption is an oversimplification as β-galactosidase is involved in the transformation of lactose to allolactose and furthermore the hydrolysis rates for lactose and allolactose are different (Huber, Wallenfels & Kurtz, 1975; Zabin & Fowler, 1978). It is known that one to four molecules of allolactose combine reversibly with the repressor R to produce the inactive repressor–inducer complex I. Zubay & Lederman (1969) showed that optimum derepression is obtained by interaction of the "functional repressor" with two inducer

molecules. These reactions can be represented by the chemical equations

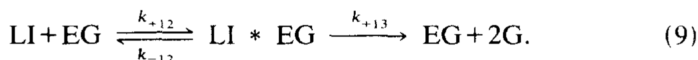
$$\text{LI} \underset{k_{-10}}{\overset{k_{+10}}{\rightleftharpoons}} \text{A} \tag{7}$$

and

$$\rho \text{A} + R \underset{k_{-11}}{\overset{k_{+11}}{\rightleftharpoons}} I, \tag{8}$$

where ρ is the number of molecules of allolactose combining with the repressor protein.

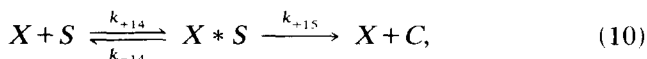
We shall assume a rapid equilibrium in equation (7) which will effectively make LI into the inducer for the induction–repression model. This assumption makes the model fit the classical induction model of Jacob & Monod (1961). In the model we want to consider the negative feedback by the metabolic endproduct of the induced gene or catabolic repression. Again as an example the *lac* operon is controlled through negative feedback by the sugar, glucose (G). Glucose is an endproduct of the metabolism of lactose. As we have noted earlier glucose has a complex effect on the control of the *lac* operon. We shall only consider its action as a catabolite repressor. We shall assume that G is formed by the following bimolecular reaction:



$$\text{LI} + \text{EG} \underset{k_{-12}}{\overset{k_{+12}}{\rightleftharpoons}} \text{LI} * \text{EG} \xrightarrow{k_{+13}} \text{EG} + 2\text{G}. \tag{9}$$

Note that although β-galactosidase breaks lactose into glucose and galactose, the galactose is readily transformed into glucose by another enzyme. This again is a simplification as there is probably a galactosyl-enzyme intermediate (Huber, Kurtz & Wallenfels, 1976; Zabin & Fowler, 1978).

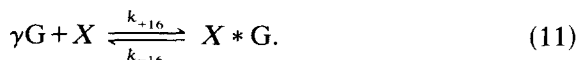
Finally, the glucose or one of its catabolic products acts as a repressor or an inhibitor of the production of c-AMP. For this model we shall not consider the possibility that glucose accelerates c-AMP catabolism rather than inhibiting production. At this state we add an unknown substance (or possibly a series of substances) X. The unknown X could be an enzyme or an mRNA leading to the production of an enzyme used in the production of C. The following equation shows how X is used in the production of C.



$$X + S \underset{k_{-14}}{\overset{k_{+14}}{\rightleftharpoons}} X * S \xrightarrow{k_{+15}} X + C, \tag{10}$$

where S is a precursor to C. S is assumed to be in constant supply. We shall also assume that one or more molecules of G combine with X to form an inactive complex $X * \text{G}$. Let γ be the number of molecules of G combining with X. The observed catabolite repression of glucose on the

production of c-AMP is given by the chemical equation



$$\gamma \mathrm{G} + X \underset{k_{-16}}{\overset{k_{+16}}{\rightleftharpoons}} X * \mathrm{G}. \tag{11}$$

In the model it will be necessary to account for loss of the various chemical species such as C, mRNA, G, EP, and EG by enzymatic degradation or dilution from cell growth. Various other compounds like NTP, AA, and R will be assumed to be in constant concentrations to simplify the model.

3. Mathematical Model for the Induction–Repression Model

In the previous section the biochemical equations were written for 24 different chemical species. We shall use basic principles from chemical kinetics with appropriate simplifying assumptions to develop the mathematical models. The mathematical models assume that the chemical species are in sufficient quantities such that a deterministic approach can be taken, i.e. differential equations can be used to model the concentrations of the chemical species. This approach has been used for the *lac* operon by Berg & Blomberg (1977).

One standard simplifying assumption is that several of the compounds are maintained at constant concentrations by the cell. We shall assume that the species NTP, AA, LE, and S satisfy this assumption. We shall also assume that the total amount of the gene OT, the total amount of the repressor protein RT, and the total amount of the unknown substance XT are maintained at constant concentrations. Let $[Z]$ denote the cellular concentration of the chemical species Z. The conservation of the genetic material is given by the equation

$$OT = [O] + [R * O] + [R * C * O] + [C * C] + [C * O * \mathrm{NTP}]. \tag{12}$$

Similarly the conservation of RT and XT is given by the following equations:

$$\begin{aligned} RT &= [R] + [R * O] + [R * C * O] + [I] \\ XT &= [X] + [X * S] + [X * G]. \end{aligned} \tag{13}$$

As the operon is only one molecule per cell, it can be assumed that the repressor protein bound to the operon represents only a small fraction of the total repressor protein. This assumption implies that RT can be approximated by the following equation:

$$RT \cong [R] + [I]. \tag{14}$$

In fact there are about ten repressors per cell (Gilbert & Muller-Hill, 1970) which means this approximation could result in a 10% error.

As both EP and EG are transcribed from the same mRNA and if they are assumed to decay at a similar rate, we may assume that [EP] equals (or is proportional) to [EG]. β-galactosidase and β-galactoside permease are stable enzymes which imply the main change in the concentrations is by dilution during cell growth. Using the law of mass action from chemical kinetics, we can write the following differential equations for the chemical species mRNA, EP, LI, G, and C:

$$\frac{d[\mathrm{mRNA}]}{dt} = k_{+5}[C * O * \mathrm{NTP}] + (k_{-6} + k_{+7})[\mathrm{AA} * \mathrm{mRNA}] - k_{+6}[\mathrm{AA}][\mathrm{mRNA}], \tag{15}$$

$$\frac{d[\mathrm{EP}]}{dt} = k_{+7}[\mathrm{AA} * \mathrm{mRNA}] + (k_{-8} + k_{+9})[\mathrm{LE} * \mathrm{EP}] - k_{+8}[\mathrm{LE}][\mathrm{EP}], \tag{16}$$

$$\frac{d[\mathrm{LI}]}{dt} = k_{+9}[\mathrm{LE} * \mathrm{EP}] + k_{-10}[\mathrm{A}] + k_{-12}[\mathrm{LI} * \mathrm{EG}] - k_{+12}[\mathrm{LI}][\mathrm{EG}] - k_{+10}[\mathrm{LI}], \tag{17}$$

$$\frac{d[\mathrm{G}]}{dt} = 2k_{+13}[\mathrm{LI} * \mathrm{EG}] + \gamma(k_{-16}[X * \mathrm{G}] - k_{+16}[X][\mathrm{G}]^{\gamma}), \tag{18}$$

$$\frac{d[C]}{dt} = k_{+15}[X * S] + k_{-3}[C * O] - k_{+3}[C][O]. \tag{19}$$

Another assumption we can make is that the equilibria of equations (1)–(3), (7), (8), and (11) are achieved very rapidly. This assumption says that the change in formation of the complex is zero. Thus as an example from equation (1) we write

$$\frac{d[R * O]}{dt} = k_{+1}[R][O] - k_{-1}[R * O] = 0.$$

From this it is easily seen that

$$[R * O] = (k_{+1}/k_{-1})[R][O]. \tag{20}$$

Similarly from the equations (2), (3), (7), (8), and (11) the following algebraic equations can be formulated:

$$[R * C * O] = (k_{+2}/k_{-2})[R][C * O], \tag{21}$$

$$[C * O] = (k_{+3}/k_{-3})[C][O], \tag{22}$$

$$[\mathrm{A}] = (k_{+10}/k_{-10})[\mathrm{LI}], \tag{23}$$

$$[I]=(k_{+11}/k_{-11})[R][\mathrm{A}]^{\rho}, \tag{24}$$

$$[X*\mathrm{G}]=(k_{+16}/k_{-16})[X][\mathrm{G}]^{\gamma}. \tag{25}$$

Another useful approximation made in enzyme kinetic problems is called the quasi-steady state approximation or the Briggs–Haldane modification of the Michaelis–Menten approximation. We shall apply this approximation to the equations (4)–(6), (9), and (10). This technique assumes the equilibrium complex in the above equations has achieved its steady-state. Using equation (4) as an example we can write

$$\frac{\mathrm{d}[C*O*\mathrm{NTP}]}{\mathrm{d}t}=k_{+4}[C*O][\mathrm{NTP}]-(k_{-4}+k_{+5})[C*O*\mathrm{NTP}]=0,$$

resulting in the algebraic equation

$$[C*O*\mathrm{NTP}]=[k_{+4}/(k_{-4}+k_{+5})][C*O][\mathrm{NTP}]. \tag{26}$$

Similarly the following algebraic equations can be written for equations (5), (6), (9), and (10):

$$[\mathrm{AA}*\mathrm{mRNA}]=[k_{+6}/(k_{-6}+k_{+7})][\mathrm{AA}][\mathrm{mRNA}], \tag{27}$$

$$[\mathrm{LE}*\mathrm{EP}]=[k_{+8}/(k_{-8}+k_{+9})][\mathrm{LE}][\mathrm{EP}], \tag{28}$$

$$[\mathrm{LI}*\mathrm{EG}]=[k_{+12}/(k_{-12}+k_{+13})][\mathrm{LI}][\mathrm{EG}], \tag{29}$$

$$[X*S]=[k_{+14}/(k_{-14}+k_{+15})][X][S]. \tag{30}$$

The induction–repression model can now be reduced to a system of five non-linear differential equations. In our model we shall assume there is a linear decay of the compounds mRNA, C, G, and EP. Combining equations (19) and (22) with a linear decay term of the form $b_1[C]$, we obtain the following:

$$\frac{\mathrm{d}[C]}{\mathrm{d}t}=k_{+15}[X*S]-b_1[C]. \tag{31}$$

Combining equations (15) and (27) with a linear decay term of the form $b_2[\mathrm{mRNA}]$, we obtain the following:

$$\frac{\mathrm{d}[\mathrm{mRNA}]}{\mathrm{d}t}=k_{+5}[C*O*\mathrm{NTP}]-b_2[\mathrm{mRNA}]. \tag{32}$$

With a linear decay term of the form $b_3[\mathrm{EP}]$ and the equations (27) and (28), equations (16) can be written as follows:

$$\frac{\mathrm{d}[\mathrm{EP}]}{\mathrm{d}t}=a_3[\mathrm{mRNA}]-b_3[\mathrm{EP}], \tag{33}$$

where $a_3 = k_{+6}k_{+7}[\mathrm{AA}]/(k_{-6}+k_{+7})$. Using equations (23), (28), and (29), we may write equation (17) as follows:

$$\frac{\mathrm{d}[\mathrm{LI}]}{\mathrm{d}t} = a_4[\mathrm{EP}] - b_4[\mathrm{LI}][\mathrm{EG}], \tag{34}$$

where $a_4 = k_{+8}k_{+9}[\mathrm{LE}]/(k_{-8}+k_{+9})$ and $b_4 = k_{+12}k_{+13}/(k_{+12}+k_{-13})$. With a linear decay term of the form $b_5[\mathrm{G}]$ and the equations (25) and (29), equation (18) can be written in the following manner:

$$\frac{\mathrm{d}[\mathrm{G}]}{\mathrm{d}t} = a_5[\mathrm{LI}][\mathrm{EG}] - b_5[\mathrm{G}], \tag{35}$$

where $a_5 = 2b_4$.

From equation (13) with equations (25) and (30) an easy rearrangement of terms gives

$$[X] = XT/(1+K_{14}[S]+K_{16}[\mathrm{G}]^{\gamma}), \tag{36}$$

where $K_{14} = k_{+14}/(k_{-14}+k_{+15})$ and $K_{16} = k_{+16}/k_{-16}$. Using the assumption that $[S]$ is a constant along with equations (30) and (36), we can simplify equation (31) to the following non-linear differential equation:

$$\frac{\mathrm{d}[C]}{\mathrm{d}t} = \frac{a_1}{(1+K_1[\mathrm{G}]^{\gamma})} - b_1[C], \tag{37}$$

where $a_1 = k_{+15}KS(XT)/(1+KS)$, $KS = K_{14}[S]$, and $K_1 = k_{+16}/\{k_{-16}(1+KS)\}$.

Equation (14) with equations (23) and (24) can be solved for $[R]$ to give

$$[R] = RT/(1+K_{10}[\mathrm{LI}]^{\rho}), \tag{38}$$

where $K_{10} = (k_{+11}/k_{-11})(k_{+10}/k_{-10})^{\rho}$. With equations (21), (22), and (26), equation (12) implies

$$OT = [O] + K1[R][C] + K2[R][C][O] + KN[C][O],$$

where $K1 = (k_{+1}/k_{-1})$, $K2 = (k_{+2}k_{+3}/k_{-2}k_{-3})$, and $KN = \{(k_{+3}/k_{-3}) + (k_{+3}k_{+4}[NTP]/(k_{-3}(k_{-4}+k_{+5}))\}$. Using equation (38) and solving for $[O]$, we see that

$$[O] = \frac{OT(1+K_{10}[\mathrm{LI}]^{\rho})}{(1+KN[C])(1+K_{10}[\mathrm{LI}]^{\rho}) + (K1+K2[C])RT}.$$

Using the above information with equations (22) and (26), we can simplify

equation (32) to

$$\frac{\mathrm{d}[\mathrm{mRNA}]}{\mathrm{d}t}=\frac{A_2[C](1+K_{10}[LI]^{\rho})}{(1+KN[C])(1+K_{10}[LI]^{\rho})+(K1+K2[C])RT}-b_2[\mathrm{mRNA}], \tag{39}$$

where $A_2=(k_{+3}k_{+4}k_{+5}[\mathrm{NTP}]OT/(k_{-3}(k_{-4}+k_{+5})))$.

From the above information we can now formulate a mathematical model for the *lac* operon. Let $x_1=[C]$, $x_2=[\mathrm{mRNA}]$, $x_3=[\mathrm{EP}]$ $(=[\mathrm{EG}]$ by assumption), $x_4=[\mathrm{LI}]$, and $x_5=[\mathrm{G}]$. In this model there are various delays to be taken into account. Let r_1 represent the delay caused by the various reactions needed for glucose to repress the production of c-AMP. Let r_2 be the amount of time required to transcribe the *lac* operon. Let r_3 be the amount of time needed for translation of the mRNA produced from the above transcription. Finally, we represent the time for transporting lactose across the cellular membrane by the delay r_4. Let $\dot{x}=\mathrm{d}x/\mathrm{d}t$. Using this notation in the equations (33)–(35), (37) and (39), we can write the following system of delay differential equations:

$$\dot{x}_1(t)=\frac{a_1}{(1+K_1(x_5(t-r_1))^{\gamma})}-b_1x_1(t), \tag{40a}$$

$$\dot{x}_2(t)=\frac{a_2x_1(t-r_2)(1+K_2(x_4(t-r_2))^{\rho})}{(1+K_3x_1(t-r_2))(1+K_4(x_4(t-r_2))^{\rho})+K_5}-b_2x_2(t), \tag{40b}$$

$$\dot{x}_3(t)=a_3x_2(t-r_3)-b_3x_3(t), \tag{40c}$$

$$\dot{x}_4(t)=a_4x_3(t-r_4)-b_4x_3(t)x_4(t), \tag{40d}$$

$$\dot{x}_5(t)=a_5x_3(t)x_4(t)-b_5x_5(t), \tag{40e}$$

where a_2, K_2, K_3, K_4 and K_5 are constants appropriately scaled from equation (39). Note that K_5 may be non-positive.

4. Modifications of the Mathematical Model

The system of differential delay equations given by equations (40) is highly non-linear. There are a couple of assumptions that can lead to a simplification of the system. The models we shall list below are based on the model given by equations (40). The assumptions used may not necessarily be well founded for our example, the *lac* operon, but their use allows a more thorough mathematical analysis than would be possible for equations (40). In turn this information helps our understanding of the system of equations given by equations (40).

The first assumption is to remove the non-linearities in equations (40a) and (40b). Instead of assuming that [EG] = [EP], we shall assume that the β-galactoside permease is the rate limiting enzyme in the reaction or in effect the β-galactosidase is in excess. Kennedy (1970) states that the transport across the cell membrane is the rate limiting reaction in the metabolism of lactose. We use this assumption to consider [EG] as a constant. With an appropriate scaling of the constants a_5 and b_4, the system of equations (40) becomes

$$\dot{x}_1(t) = \frac{a_1}{(1+K_1(x_5(t-r_1))^{\gamma})} - b_1 x_1(t), \tag{41a}$$

$$\dot{x}_2(t) = \frac{a_2 x_1(t-r_2)(1+K_2(x_4(t-r_2))^{\rho})}{(1+K_3 x_1(t-r_2))(1+K_4(x_4(t-r_2))^{\rho})+K_5} - b_2 x_2(t), \tag{41b}$$

$$\dot{x}_3(t) = a_3 x_2(t-r_3) - b_3 x_3(t), \tag{41c}$$

$$\dot{x}_4(t) = a_4 x_3(t-r_4) - b_4 x_4(t), \tag{41d}$$

$$\dot{x}_5(t) = a_5 x_4(t) - b_5 x_5(t). \tag{41e}$$

A second simplifying assumption is if the constant $K_3 \ll 1$ in equation (41b), then the x_1 term in the denominator can be omitted. This would change equation (41b) into the following:

$$\dot{x}_2(t) = \frac{a_2 x_1(t-r_2)(1+K_2(x_4(t-r_2))^{\rho})}{(1+K_4(x_4(t-r_2))^{\rho})} - b_2 x_2(t), \tag{42b}$$

rescaling a_2 and K_4. Equations (42b), (41c), and (41d) closely resemble the induction models found in the literature (e.g. Griffith, 1968*b*; Othmer, 1976; Banks & Mahaffy, 1979). The principle difference is the appearance of the $x_1(t-r_2)$ in the non-linear growth term on the right hand side of the equation (42b). Equations (41b) (or 42b)), (41c), and (41d) represent the inner induction loop of our model. Equations (41a) and (41e) form the outer control loop. Note that these equations are in the form found in the literature for repression models (e.g. Griffith, 1968*a*; Othmer, 1976; Banks & Mahaffy, 1979). Combining equations (41a), (42b), (41c), (41d), and (41e), we obtain a model for an induction process controlled by a repression process. Note that this is an oversimplification of the model for the *lac* operon.

The equations (40) can be reduced to system of delay differential equations with only three delays by a change of variables as seen in an der Heiden (1979) or Mahaffy (1980). Furthermore by rescaling the state and time variables to non-dimensional units we can eliminate several of the

parameters. If we let z_i denote the rescaled state variables, t be the rescaled time variable, and R_i be the rescaled delays, then the system becomes

$$\begin{aligned}
\dot{z}_1(t) &= \frac{1}{1+(z_5(t-R_1))^\gamma} - b_1 z_1(t),\\
\dot{z}_2(t) &= \frac{z_1(t)[1+K_2(z_4(t-R_2))^\rho]}{(1+K_3 z_1(t))(1+K_4(z_4(t-R_2))^\rho)+K_5} - b_2 z_2(t),\\
\dot{z}_3(t) &= z_2(t) - b_3 z_3(t),\\
\dot{z}_4(t) &= z_3(t-R_3) - b_4 z_3(t) z_4(t),\\
\dot{z}_5(t) &= z_3(t) z_4(t) - b_5 z_5(t),
\end{aligned} \tag{43}$$

where the b_is and K_is are suitably rescaled.

Similarly a change of variables can make the simplified induction–repression model given by equations (41a), (42b), (41c), (41d) and (41e) into a system of delay differential equations with only two delays. As before a rescaling of the state and time variables to non-dimensional units can eliminate six of the parameters, so that the following system of equations is obtained:

$$\begin{aligned}
\dot{z}_1(t) &= \frac{1}{1+(z_5(t-T_1))^\gamma} - b_1 z_1(t),\\
\dot{z}_2(t) &= \frac{z_1(t)[1+K_2(z_4(t-T_2))^\rho]}{[1+K_4(z_4(t-T_2))^\rho]} - b_2 z_2(t),\\
\dot{z}_3(t) &= z_2(t) - b_3 z_3(t),\\
\dot{z}_4(t) &= z_3(t) - b_4 z_4(t),\\
\dot{z}_5(t) &= z_4(t) - b_5 z_5(t),
\end{aligned} \tag{44}$$

where z_i denotes the rescaled state variable, t is the rescaled time variable, T_i are the shifted delays, and the b_is and K_is are suitably rescaled. This system with only two delays allows a more detailed mathematical analysis.

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