On the Stability of the Kinetics of a Certain Class of Biomolecular Reactions

A. D. Nazaev
Committee on Mathematical Biology, The University of Chicago

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Summary. By means of a formal kinetic model, an analysis of the behavior of a certain type of unbranched sequences of biomolecular reactions is made. The main results are in (i) the characterization of the steady-state, (ii) the specification of a condition under which the largest physically admissible invariant set, containing the steady-state as invariant subset, can be obtained, and (iii) the deduction of parameter restrictions sufficient to assure asymptotic stability in the large in the given invariant set with respect to the steady-state.

1. Introduction

The present work is a study of the kinetics of intracellular biomolecular synthesis involving transcription from a particular locus, L, of DNA and translation to a single polypeptide, P, for which the locus codes, the polypeptide then becoming the precursor in a biomolecular sequence of reactions involving r metabolites, $M^{(k)}$ ($k = 1, \ldots, r < \infty$), with the molecules of the terminal metabolite, $M^{(r)}$, exerting a regulative influence on the locus L through a reversible complexing reaction. We shall be interested in a formal kinetic model of a class of such biomolecular sequences, in particular with respect to its steady-state, its associated invariant set and its stability behavior.

A sketch of the most important steps involved in the processes under study may be given as follows (Vogel and Vogel, 1967; Schweet and Heintz, 1966). Consider a particular locus, L, on one strand of a double-stranded DNA molecule. The biomolecular sequence is initiated when mRNA copies of L are synthesized from a pool of ribonucleotides through the action of DNA-dependent RNA-polymerase.

A polyribosome complex is formed on an mRNA molecule by proper orientation of ribosomes along it. Aminoacyl-tRNA molecules, derived from an intracellular pool, then sequentially get bound to the active site(s) on the polyribosome complex to form the polypeptide chain from the N- to the C-terminus under the action of peptidyl transferase and one or more ‘translocases’, the exact ordering being dictated by complementarity with respect to the base sequence of the mRNA molecule. Molecules of the polypeptide P are formed on the mRNA-ribosome complex in this manner.

Consider now the situation where this primary polypeptide becomes a precursor in a chain of enzymatically mediated biomolecular reactions involving arbitrarily many metabolites. In the sequel, we shall speak interchangeably of biomolecular sequences and biosynthetic systems when we wish to refer to such
chains. Under dynamic intracellular conditions, RNA molecules are synthesized as well as degraded. Likewise, molecules of the synthesized polypeptide, as well as those of the metabolites for which it is the precursor, either participate in the reactions or are otherwise ultimately degraded.

We now in particular take the class of biomolecular sequences which are unbranched, and assume that there are \( r \) metabolites in the sequence, \( M^{(k)} \) \((k = 1, \ldots, r < \infty)\), with the last metabolite, \( M^{(r)} \), exerting a regulatory influence on the locus \( L \) through a reversible complexing reaction to be specified below.

2. The Kinetic Equations

The following assumptions will be made in deriving the kinetic equations of a formal model of the class of biomolecular sequences described in the previous section.

(i) The time rate of degradation of mRNA molecules is proportional to their concentration.

(ii) The time rate of increase in concentration of the polypeptide \( P \) is directly proportional to the concentration of mRNA.

(iii) The time rate of degradation of polypeptide molecules is directly proportional to the concentration of the polypeptide.

(iv) The time rate of increase in concentration of the molecules of the first metabolite, \( M^{(1)} \), is directly proportional to the concentration of \( P \).

(v) The time rate of increase in concentration of the molecules of the \( j^{th} \) metabolite, \( M^{(j)} \), is directly proportional to the concentration of the \((j-1)^{st}\), \( M^{(j-1)} \), \( j = 2, \ldots, r \).

(vi) The time rate of degradation of the molecules of \( M^{(k)} \), \( k = 1, \ldots, r \), is directly proportional to their concentrations.

(vii) The time rate at which molecules of the terminal metabolite, \( M^{(r)} \), are utilized in other reactions is directly proportional to their concentration.

(viii) Regulation of the DNA locus \( L \) takes the following form. The presence of free molecules of \( M^{(r)} \) exerts a specific inhibitory influence on the locus by hindering reversibly the transcription of mRNA molecules from it. If \( \lambda \) molecules (\( \lambda \) being of course integral and positive) are required to complex the locus \( L \), the reaction may be represented as

\[
L + \lambda \, M^{(r)} \rightleftharpoons [LM^{(r)}].
\]

The complexed locus \([LM^{(r)}]\) is considered as being incapable of acting as a template for the synthesis of mRNA.

Let \( S_1(t) \) denote the intracellular concentration of mRNA molecules (synthesized on the locus \( L \)) coded for the polypeptide \( P \), the intracellular concentration of the latter being denoted by \( S_2(t) \). And let \( Q_k(t) \) be the intracellular concentration of the metabolites \( M^{(k)} \) \((k = 1, \ldots, r)\).

From assumption (viii), it follows that the fraction of time that the locus \( L \) is not complexed is given by the expression

\[
\frac{1}{1 + \delta[Q_r(t)]^2},
\]

where \( \delta > 0 \) is the equilibrium constant for the reaction (1).