BASIC AND SIMPLE MATHEMATICAL MODEL
OF COUPLED TRANSCRIPTION, TRANSLATION AND
DEGRADATION

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Abstract
Synthesis of proteins is one of the most fundamental biological processes, which consumes a significant amount of cellular resources. Despite many efforts to produce detailed mechanistic mathematical models of translation, no basic and simple kinetic model of mRNA lifecycle (transcription, translation and degradation) exists. We build such a model by lumping multiple states of translated mRNA into few dynamical variables and introducing a pool of translating ribosomes. The basic and simple model can be extended, if necessary, to take into account various phenomena such as the interaction between translating ribosomes or regulation of translation by microRNA. The model can be used as a building block (translation module) for more complex models of cellular processes.
Introduction

Production of proteins is one of most fundamental cellular processes, taking up to 75% of cellular resources in terms of chemical energy, in simple microbes [Harold, 1986].

The translation-transcription process with the description of the most basic "elementary" processes consists in:

1) production of mRNA molecules,
2) initiation of these molecules by circularization with help of initiation factors,
3) initiation of translation, recruiting the small ribosomal subunit
4) assembly of full ribosomes
5) elongation, i.e. movement of ribosomes along mRNA with production of protein
6) termination of translation
7) degradation of mRNA molecules
8) degradation of proteins

Certain complexity in the mathematical formulation of this process arises when one tries to take into account the phenomenon of polysome first described in (Warner et al, 1963), when several ribosomes are producing peptides on a single mRNA at the same time. This leads to multiplicity of possible states of mRNA with various numbers of ribosomes and potentially different dynamics, interaction between ribosomes and other difficulties. The process of translation is a subject of mathematical modeling since long time ago (e.g., see (Singh, 1996)). For a recent review of existing mathematical efforts in this direction, see (von der Haar, 2012).

Nevertheless, no basic and simple kinetic description of the process involving transcription, translation and degradation was suggested until so far.

In the following we start with a 1) detailed mechanistic description of the translation process with explicit representation of every state of translated mRNA, followed by 2) deriving the simplest and basic kinetic model of coupled transcription, translation and degradation, and 3) extending this model in order to take into account various effects. In this paper, the extensions will describe the saturation of mRNA initiation rate, effects of ribosome interactions, regulation of translation by microRNA.

The basic model is constructed by 1) correct lumping of the detailed model states and by 2) separating the descriptions of ribosomal turnover and the initiation through introducing a pool of translating ribosomes. The simplest model remains linear under assumption of that the local concentrations of ribosomal subunits or initiation factors remain constant or changes relatively slowly. To avoid non-physiological properties (such as a possibility of infinite number of ribosomes per mRNA), we modify the model by introducing unavoidable delays in the initiation
of ribosome and the effects of ribosome interactions. In this form, the model becomes more realistic but non-linear in some extensions.

More complex phenomena related to translation can be taken into account in direct simulatory models of the detailed representation of translation at the cost of more difficult analytical analysis of the model (see an example of explicit translation simulation as a module in the whole-cell modeling of M. Plasmodium (Karr et al, 2012)).

Results

Detailed model of translation

Let us introduce the following notations:

- \( L \) – length of mRNA (in nucleotides);
- \( l_m \) – length occupied on mRNA by fully assembled ribosome (in nucleotides);
- \( k_t \) – rate constant of production of mRNA molecules;
- \( k_d \) – rate constant of degradation of mRNA molecules;
- \( k_r \) – speed of movement of translating ribosome along mRNA (nucleotise/sec);
- \( IF \) – various initiation factors;
- \( S40 \) – small ribosome component;
- \( S60 \) – large ribosome component.

Further we will use squared brackets to denote the concentrations of the corresponding molecular entities: for example, \([S40]\) will denote the local concentration of S40 ribosomal subunits. For the amounts of the components we keep the same notations as for the components themselves. Thus, \( R \) is amount of amount of ribosomes and the total amount of mRNA molecules is \( MT \).

The simplest assumption about the production and destruction of mRNA is that the degradation process does not depend on the state of mRNA. Under this assumption the total pool of mRNAs is produced at rate \( k_t \) and destroyed with rate constant \( k_d \), i.e. its dynamics is simple and autonomous:

\[
\frac{dMT}{dt} = k_t - k_d \times MT .
\]

It is worth to notice that the production rate \( k_t \) is an extensive quantity (it scales with the total volume of the system) whereas all rate constants are intensive ones.

The total pool of mRNA molecules can be separated in sub-pools of mRNA molecules in different states:
$R_0$ – mRNA molecules in non-initiated state (not ready for translation)

$R_0$ – mRNA molecules in initiated state (ready for translation, with 40S subunit sitting at the mRNA)

$R_1$ – mRNA molecules with one single ribosome assembled and moving along the mRNA

$R_1$ – mRNA molecules with one ribosome assembled and initiated for new incoming ribosome

$R_2$ – mRNA molecules with two ribosomes assembled and moving along the mRNA

$R_2$ – mRNA molecules with two ribosomes assembled and initiated for new incoming ribosome

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$R_{n_{\text{max}}}$ – mRNA molecules with $n_{\text{max}}$ ribosomes assembled and moving along the mRNA

$R_{n_{\text{max}}}$ – mRNA molecules with $n_{\text{max}}$ ribosomes assembled and initiated for new incoming ribosome

The sum of all sub-pools of mRNA should be equal to $MT$:

$$MT = \sum_{i=0}^{n_{\text{max}}}(R_i + I_i)$$

The number $n_{\text{max}}$ is defined as the maximum number of ribosomes able to sit on mRNA: it may be roughly evaluated as

$$n_{\text{max}} = L / l_m.$$  

Schematically, the process of translation can be represented as in Figure 1.

Figure 1. Schematic process of detailed translation representation. It requires $2 \times (n_{\text{max}}+1)$ mRNA states.

The time of passage of one ribosome along mRNA may be evaluated as
\( t_p = \frac{L}{k_r} \),

hence, the reaction rate constant of protein production and subsequent release of ribosomes from mRNA (shown in Figure 1 by backward arrows) may be evaluated as:

\[ k_3 = \frac{k_r}{L} . \]

The transformation of states is described by the following chemical equations:

\[ R_i \rightarrow R_i \] (with rate constant \( k_1 \)), \( i = 0 \ldots \text{nmax} \)

\[ R_i \rightarrow R_{i+1} \] (with rate constant \( k_2 \)), \( i = 0 \ldots \text{nmax}-1 \)

\[ R_i \rightarrow R_{i-1} \] (with rate constant \( k_3 \)), \( i = 1 \ldots \text{nmax} \)

\[ R_i \rightarrow R_{i-1} \] (with rate constant \( k_3 \)), \( i = 1 \ldots \text{nmax} \)

\[ R_i \rightarrow R_{i+1} \] (with rate constant \( k_{rd} \)), \( i = 1 \ldots \text{nmax} \)

\[ R_i \rightarrow R_{i-1} \] (with rate constant \( k_{rd} \)), \( i = 1 \ldots \text{nmax} \)

**Basic model of translation, constructed by lumping the states of the detailed model**

To avoid using \( 2 \times (\text{nmax}+1) \) states (which potentially can be large) to represent translation, we lump the description of the detailed process in the following way.

We denote

\( M \) – amount of mRNA with translation initiation site not occupied by assembling ribosome,

\( F \) – amount of mRNA with translation initiation site occupied by assembling ribosome,

\( R \) – amount of ribosomes sitting on mRNA synthesizing proteins,

\( P \) – amount of proteins.

In terms of \( R_i \) and \( R_i \) variables, \( M \) and \( F \) represent the lumped values:

\[ M = \sum_{i=0}^{\text{nmax}} R_i , \quad F = \sum_{i=0}^{\text{nmax}} R_i \quad \text{and} \quad MT = M + F. \]

There are two lumped reactions and two reactions representing the turnover of ribosomes (as a result of translation termination and protein synthesis or spontaneous ribosome drop-off from mRNA without protein production):

\( M \rightarrow F \) with reaction rate constant \( k_f \),

\( F \rightarrow M + R \) with reaction rate constant \( k_2 \),

\( R \rightarrow \text{null} \) with reaction rate constant \( k_3 \),

\( R \rightarrow \text{null} \) with reaction rate constant \( k_{rd}+k_d \) (ribosome drop-off and degradation without protein production).
The reaction network describing transcription, translation and mRNA degradation is represented in Figure 2. We will denote this model as $\mathcal{M}_0$.

The corresponding list of equations is

\[
\begin{align*}
\dot{M} &= k_t - k_d M - k_1 M + k_2 F \\
\dot{F} &= k_1 M - k_d F - k_2 F \\
\dot{R} &= k_2 F - k_3 R - k_{rd} R - k_d R \\
\dot{P} &= k_3 R - k_p P \\
\end{align*}
\]

which has the following solution for zero initial condition $M(0) = F(0) = R(0) = P(0) = 0$

\[
M(t) = \frac{k_t}{k_d} \frac{1}{(k_1 + k_2 + k_d)(k_1 + k_2)} \left[ (k_1 + k_2)(k_2 + k_d) - k_2(k_1 + k_2 + k_d)e^{-k_d t} - k_1 k_d e^{-(k_1 + k_2 + k_d)t} \right]
\]

\[
F(t) = \frac{k_t}{k_d} \frac{1}{(k_1 + k_2 + k_d)(k_1 + k_2)} \left[ k_1(k_2 + k_d) - k_1(k_1 + k_2 + k_d)e^{-k_d t} + k_1 k_d e^{-(k_1 + k_2 + k_d)t} \right],
\]

\[
R(t) = \frac{k_t}{k_d} \frac{k_1 k_2}{(k_3 + k_{rd} + k_d)(k_1 + k_2 + k_d)(k_1 + k_2)} \times \left[ (k_1 + k_2) - \frac{(k_3 + k_{rd} + k_d)(k_1 + k_2 + k_d)}{(k_3 + k_{rd})} e^{-k_d t} + \frac{(k_3 + k_{rd} + k_d)k_d}{(k_3 + k_{rd} - k_1 - k_2)} e^{-(k_1 + k_2 + k_d)t} - (k_1 + k_2)e^{-(k_1 + k_{rd} + k_d)t} \right],
\]

\[
P(t) = \frac{k_t}{k_d} \frac{k_1 k_2 k_3}{k_p(k_1 + k_2 + k_d)(k_3 + k_{rd} + k_d)} \left[ -e^{-k_d t} + e^{-(k_1 + k_2 + k_d)t} - e^{-(k_3 + k_{rd} + k_d)t} - e^{-k_p t} \right].
\]

(2)

![Figure 2. Basic and the simplest model $\mathcal{M}_0$ of translation process.](image)

The simplest model $\mathcal{M}_0$ can be made more complex if some particular aspects of translation are needed to be represented in more details. Below we build several such modifications. In the model $\mathcal{M}_0'$ we explicitly model the first round of mRNA initiation which can be longer than the
consequent rounds of 40S recruitment and production of translating ribosomes in the pool. In the model $\mathcal{M}_1$ we explicitly model the step of binding of 40S and 60S subunits to mRNA. In the model $\mathcal{M}_1'$ we also explicitly add the binding of the initiation factors. In the model $\mathcal{M}_0'$reg we introduce the effect of irreversible binding of a regulatory molecule to mRNA which can be, for example, a microRNA.

$\mathcal{M}_0'$ model: Distinguishing the initial initiation stage in the basic model

Specific states of mRNA such as $R_0$ (free mRNA) and $R_0$ (initiated mRNA) can be separately represented in the model. Let us denote the amount of mRNA in these states as $M_0 = R_0$ and $F_0 = R_0$. The corresponding reaction network is shown in Figure 3. This model is able to represent specific states of just produced, non-initiated mRNA. This model contains two additional parameters: $k_{01}$ and $k_{02}$, which are rate constants of the first round of mRNA initiation and firing the first assembled ribosome into the pool. Evidently, these constants cannot be smaller than $k_1$ and $k_2$, because they include some additional events: $k_1$ corresponds to recruiting 40S while $k_{01}$ corresponds to initiating the new-born mRNA and recruiting 40S on it. Thus, typically $k_{01} << k_1$.

If $k_{02} << k_2$ then this can represent translation with membrane-bound ribosomes or SRP cycle (Singh, 1996), when there is a transient translation arrest in the initiated monosome state (the very beginning of the translation).

Separating $M_0$ and $F_0$ states also allows estimating the average number of ribosomes $RB$ sitting on an initiated mRNA (the pool represented by $M$ and $F$ states in $\mathcal{M}_0'$).

The corresponding system of equations is
\[
\begin{align*}
\frac{dM_0}{dt} &= k_i - (k_d + k_{01})M_0, \\
\frac{dF_0}{dt} &= k_{01}M_0 - (k_d + k_{02})F_0, \\
\frac{dM}{dt} &= k_{02}F_0 + k_2F - (k_d + k_1)M, \\
\frac{dF}{dt} &= k_1M - (k_d + k_2)F, \\
\frac{dR}{dt} &= k_{02}F_0 + k_2F - (k_d + k_{rd} + k_3)R, \\
\frac{dP}{dt} &= k_3R - k_pP
\end{align*}
\]

which has the following steady-state solution:

\[
M_0 = \frac{k_i}{k_{01} + k_d}, \quad F_0 = \frac{k_i k_{01}}{(k_{01} + k_d)(k_{02} + k_d)},
\]

\[
M = \frac{k_i k_{01} k_{02} (k_2 + k_d)}{k_d (k_{01} + k_d)(k_{02} + k_d)(k_1 + k_2 + k_d)}, \quad F = \frac{k_i k_{01} k_{02} k_1}{k_d (k_{01} + k_d)(k_{02} + k_d)(k_1 + k_2 + k_d)},
\]

\[
R = \frac{k_i k_{01} k_{02} (k_1 + k_d)(k_2 + k_d)}{k_d (k_{01} + k_d)(k_{02} + k_d)(k_1 + k_2 + k_d)(k_3 + k_d + k_{rd})},
\]

\[
P = \frac{k_3 k_i}{k_p k_d} \frac{k_0 k_{01} k_{02} (k_1 + k_d)(k_2 + k_d)}{(k_{01} + k_d)(k_{02} + k_d)(k_1 + k_2 + k_d)(k_3 + k_d + k_{rd})}.
\]

\[
MT = M_0 + F_0 + M + F = \frac{k_i}{k_d},
\]

\[
RB = \frac{R}{M + F} = \frac{(k_1 + k_d)(k_2 + k_d)}{(k_1 + k_2 + k_d)(k_3 + k_d + k_{rd})}.
\]

The relaxation times are

\[
rt_{M_0} = \frac{1}{k_{01} + k_d}, \quad rt_{F_0} = \frac{1}{\min(k_{01} + k_d, k_{02} + k_d)},
\]

\[
rt_M = rt_F = \frac{1}{k_d}, \quad rt_R = \frac{1}{k_d}, \quad rt_P = \frac{1}{\min(k_d, k_p)}.
\]

(The \(M-F\) subsystem has the kinetic matrix with eigenvalues \(-k_d\) and \(-k_{rd} - k_1 - k_2\).)

Models \(\mathfrak{M}_1\) and \(\mathfrak{M}_1'\): Explicit representation of 40S, 60S and initiation factors binding
One of the undesired features of the simplest translation models $\mathcal{M}_0$ and $\mathcal{M}_0'$ is a possibility of unrealistic increase of the number of translating ribosomes in the pool. The kinetic rate constants $k_1$ and $k_2$ implicitly include the concentrations (not amounts) of 40S and 60S subunits correspondingly. Increasing these concentrations might lead to the unlimited growth of the steady-state amount of ribosomes (2).

More detailed representation of reaction $M \rightarrow F$ includes the intermediate step of reversible binding of mRNA to the small ribosomal subunit $M + 40S \rightarrow M:40S$ and the scanning step during which 40S bound to mRNA search for the start codon: $M:40S \rightarrow F$, where $F$ represents a state of mRNA with 40S positioned at the start codon and ready to recruit 60S. The time needed for finding the start codon ($\sim 1/k_a$) is a complex function of presence of certain initiation factors and, possibly, length and the secondary structure of 5'UTR.

Similar to $\mathcal{M}_0'$, we can decouple the two initial states of mRNA in $\mathcal{M}_1$ and produce the model $\mathcal{M}_1'$, in which binding of initiation factors ($IF_1$ and $IF_2$) can be represented explicitly (Figure 5). In this model we distinguish two types of initiation factors: $IF_1$ initiate mRNA by binding to the cap structure, poly-A tail, etc.; $IF_2$ initiate assembly of ribosomes and can be RNA helicases or other helper molecules [Manojlovic and Stefanovic, 2012]. $IF_1$ factors are released only when the initiated states of mRNA (all besides $M_0$) are degraded. $IF_2$ are released in the end of each ribosome assembly.

It is important to make a notice on the usage and recycling of 40S, 60S and IFs. All these molecules make a pool of resources (together with ATP and GTP, aminoacids, tRNAs, etc.) shared between many protein syntheses in the whole cell. The equations (1), (3) are written down for amounts of the corresponding proteins, while 40S, 60S and IFs are consumed with the rates proportional to their local concentrations (Figure 5). 40S, 60S and IFs molecules are returned to the pool of cellular resources in each act of mRNA degradation (besides in the newly born $M_0$ state) with rate constant $k_{dr}$, release of ribosomes from mRNA with rate constants $k_d$ and $k_{dr}$, in backward reactions of 40S detachment from mRNA with rate constants $k_1, k_{01}$ (not shown explicitly in Figure 5), in releasing a new translating ribosome with the rate constants $k_2, k_{02}$.

We assume that each individual protein synthesis does not significantly change the pool of cellular resources and, therefore, the local concentrations of 40S, 60S and IFs remain constant. With such quite a realistic assumption, the models remain linear and analytically tractable. However, this might not be completely satisfactory approximation for the in vitro cell-free systems for studying translation, when the amounts of 40S or 60S or IFs are made comparable to the amounts of the translated mRNA. In this case recycling of ribosomal subunits and initiation factors might be a limiting (and fast) process, thus it should be represented explicitly, taking into account the effective volume occupied by 40S or 60S or IFs in the system (because the kinetic rates of resources release give the amount of the released translation factors while their consumption rates are proportional to their concentrations).
Figure 4. Reaction network representing translation process with explicit presentation of 40S and 60S binding (model M1).

Figure 5. Reaction network representing translation process with explicit presentation of 40S, 60S and initiation factors (IF) binding (model M1').

Model M0’reg: extending the basic model of translation with microRNA-based regulation

Let us assume that the translation process can be regulated by a molecule which can irreversibly bind to mRNA and, as a result, change any kinetic rate of translation. Typical example of such a molecule is microRNA [Morozova et al, 2012], so we will call it like this further.

For our purposes (representing microRNA-based regulation), it is important to distinguish states $M_0$ and $F_0$ to be able to represent the initiation of mRNA and the effect of microRNA on the initiation process. MicroRNA can act on $k_{01}$ step ($M_0 \rightarrow F_0$), thus inhibiting the early initiation process, or on $k_1$ step ($M \rightarrow F$), thus, inhibiting step of 40S binding on already initiated mRNA, or on $k_2$ step ($F \rightarrow M+R$), thus inhibiting ribosome assembly process [Morozova et al, 2012].

To take into account the action of microRNA on translation, the model of translation shown in Figure 3 is supplied with mRNA states representing mRNA with a microRNA bound to it (states $M'_0$, $F'_0$, $M'$, $F'$, $R'$). The rate of microRNA binding is $k_p$ which determines irreversible conversion of the microRNA-free states (without prime) to microRNA-bound states (primed).
The corresponding rate constants which might be different from normal translation process are marked with prime symbol as well. In addition, we introduce a special $B$ state which describes reversible capturing of mRNA in P-bodies, where they can be specifically degraded at a higher rate $k_{bd}$ than during the microRNA-free translation.

The $\mathcal{M}_0^{\text{reg}}$ model was used in (Morozova et al, 2012) to produce the kinetic signatures of nine different mechanisms of microRNA action or their combinations.

![Figure 6. The model $\mathcal{M}_0^{\text{reg}}$ of miRNA-based regulation (Morozova et al, 2012).](image)

**Other possible model extensions**

The basic lumped model can serve as a basis for other model extensions by explicit splitting of particular states from the lumped states and other modifications. Let us list several possible scenarios:

1) More explicit representation of translation termination or elongation, description of ribosome stalling phenomenon.

2) More detailed representation of the mRNA initiation process. For example, formation of the M0:IF1:40S complex in Figure 5 should proceed in several elementary steps, with particular role and order of binding of scaffold initiation proteins and other initiation factors, with subsequent recruitment of 40S.

3) Description of phenomena connected with uneven distribution of ribosomes along mRNA, such as described in recent literature on explicit studies of ribosome positioning on mRNAs (Ingolia et al, 2009).

4) Explicit modeling of the mRNA codon usage.

5) Mean-field models of the ribosomes’ interaction: The simplest method to include the interaction of ribosomes in the lumped model is a dependence of the ribosome drop-off constant $k_{rd}$ on the average concentration $\theta$ of the ribosomes per initiated molecule of
mRNA: \( k_{rd} = k_{rd}(\theta) \). For example, for the scheme presented in Figure 3 it may be \( k_{rd}(\theta) = a/(b - \theta) \), where \( \theta = R/(M + F) \). Example of such an effect is

6) Mean-field models of how the property of the mRNA (such as its stability) might change depending on the state and also on the history of mRNA. For example, one can imagine a (very hypothetical) version of mRNA kinetics with “mRNA aging” such as each new round of translation makes mRNA more fragile and prone to destruction. Or in opposite, mRNA can become more stable with ribosomes sitting on it.

7) Modeling distribution of model parameters, leading to existence of population of mRNAs with different speeds of different steps of translation.

8) Explicit modeling of competition of various protein syntheses processes for resources (ribosomal subunits and initiation factors). The most interesting is to include in this picture the production of the resources themselves (transcription, translation, degradation), which will introduce complex global regulatory feedbacks.

**Translation limiting properties of the \( \mathbb{M}1' \) model**

In order to illustrate what distinguishes two particular translation models described above, we performed a numerical experiment in which we varied the concentrations of ribosomal subunits and studied their effect on the average number of translating ribosomes per mRNA. We compared two models \( \mathbb{M}0' \) and \( \mathbb{M}1' \), without and with an intermediate state of mRNA bound to 40S ribosomal subunit but with 40S not yet positioned at the start codon. Our purpose is to demonstrate two points: 1) that the step of late initiation might be very sensitive parameter and lead to efficient regulation of translation (which is consistent with some recent experimental findings [Cannell et al, 2008]); 2) that without this step a simpler model \( \mathbb{M}0' \) can lead to non-physiological unlimited growth of translating ribosomes per mRNA (Figure 7).

Two sets of parameter values used for numerical simulation are provided as SBTOOLBOX text files provided in the Appendix. As one can see from Figure 7, the steady state value of the average number of translating ribosomes per mRNA is not limited in the model \( \mathbb{M}0' \), if the concentrations of small and large ribosomal subunits are increased simultaneously. Increasing only concentration of 60S with fixed concentration of 40S is not sufficient: to increase the number of complexes one has to supply the system with both components.

By contrast, in the model \( \mathbb{M}1' \), simultaneous increase in the concentrations of 40S and 60S makes \( RB \) insensitive of them (Figure 7, right plot). This can be easily understood from the model shown in Figures 4 and 5. If one assumes that the rates of mRNA degradation and synthesis are slower than the translation rate then it is easy to show that the steady-state value of the average number of translating ribosomes per mRNA is

\[
RB = \frac{1}{k_3} \times \frac{k_j k_i^+ k_2[IF1][IF2][40S][60S]}{k_2[60S](k_a[IF2] + k_1^-) + k_i^+ [IF1][40S](k_2[60S] + k_a[IF2])}. \tag{6}
\]
Hence, if both ribosomal subunits are in excess then

\[ RB \big|_{[60S][40S]} = \frac{k_2 [IF2]}{k_3}. \]  

(7)

This is the limiting value of the average number of translating ribosomes per mRNA in the models \( \mathbb{M}1 \) and \( \mathbb{M}1' \).

Formula (7) has an important biological consequence: in the excess of ribosomal subunits the most sensitive parameter of protein synthesis (which is determined by \( RB \)) is the availability (or, equivalently, efficiency) of the initiation factors facilitating fixation of 40S bound to mRNA at the start codon (collectively denoted as \( IF2 \) in Figure 6). Good candidates for this type of initiation factors are RNA helicases whose role is to disentangle the 5'UTR regions of mRNA [Cannell et al, 2008; Manojlovic and Stefanovic, 2012]. The early initiation factors, collectively denoted as \( IF1 \) in Figure 6, can play less important role, if the ribosomal subunits are in excess (they do not enter into (7)).

Of course, if both initiation factors are in excess then there is saturation with respect to their values and for fixed concentrations of the ribosomal subunits we get

\[ RB \big|_{[IF1][IF2]} = \frac{k_2 [40S][60S]}{k_3}. \]

Therefore, saturation with respect to ribosomal subunits and initiation factor concentrations is not symmetric: the limiting value with respect to infinite increase of initiation factors depends on both 40S and 60S concentrations while the limiting value with respect to infinite increase of ribosomal subunits depends only on the concentration of \( IF2 \).

Figure 7. Number of translating ribosomes per mRNA \( (RB) \) in \( \mathbb{M}0' \) and \( \mathbb{M}1' \) models of translation as a function of concentrations of small \( (S40) \) and large \( (S60) \) ribosomal subunits for fixed concentrations of the initiation factors.
Discussion

The purpose of this work is somehow unusual. We do not construct yet another model of translation to fit to some experimental observations or to make new predictions. Instead, as a tool, we suggest a hierarchy of mathematical models of translation of increasing complexity. We even do not prove or disprove these models but, instead, say that each of them might be useful in a particular modeling context. Moreover, we outline how these models can be complexified almost infinitely, if some phenomenon is needed to be grasped in more details.

We start from a very simple kinetic model of translation which, however, describes a quite complex and detailed kinetics shown in Figure 1. This simplicity becomes possible because of two modeling tricks: 1) lumping many states in one dynamic variable, and 2) introducing a pool of translating ribosomes. The resulting model has a simple mechanistical analogy with closing and opening door (Figure 8).

Two simple kinetic models of translation were introduced before in (Nissan and Parker, 2008): however, they were introduced there ad hoc, without strict derivation from the detailed translation kinetics. As a matter of fact, these models do not allow taking into account neither degradation of mRNA nor existence of polysomes.

Each basic model can be compared to existing experimental results on translation. Of course, there will be always discrepancies between experiment and the theory. However, classifying experimental observations accordingly to the hierarchy of translation models is a meaningful task by itself. Each basic model should stimulate the search of the effects which cannot be covered by this model.

The basic and simple model (a set of models, to be more exact) of translation that we constructed here can be used as a module in the future more complex and probably whole-cell computational models. The only existing whole-cell mathematical model of cellular biochemistry (Karr et al, 2012) simulates translation in agent-based manner, by explicit representation of all cellular ribosomes and mRNA. This approach does not scale up to more complex cells (there are few thousands of ribosomes and mRNAs in the simplest microbe, but in mammalian cells this number is at least 1000-fold larger). Thus, kinetic models quantitatively representing translation of large quantities of mRNA will be needed. The advantages are quite evident: availability of explicit analytic expressions for the steady states and relaxation dynamics and knowledge of sensitive and rate-limiting parameters which should be estimated quite precisely.
Figure 8. A mechanistic interpretation of the simplest model of translation M0. A mRNA is a place of translation which can exist in “open” (M) and “closed” (F) states. When the place is “open” it can accept a small ribosomal subunit, after which the place is “closed” until the large ribosomal subunit is recruited and the assembled ribosome is released into the pool of translating ribosomes.

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Appendix. Supplementary information

Definition of kinetic rate constants

$k_{01}$ – rate constant of mRNA molecules initiation (adding cap structure, circularization, collecting initiation factors at mRNA, etc.), we will call it early initiation.

$k_1$ – rate constant of translation is initiated on already inititated mRNAs (molecules/sec). By this we mean rate of 40S subunit binding and shifting to the start codon.

$k_2$ – rate constant of ribosome assembly, including possible transient arrest of ribosomes before starting translation (molecules/sec)

$k_r$ – speed at which fully assembled ribosomes moves along mRNA (nucleotides/sec); this speed include the rate of translation termination.

$k_{rd}$ – rate constant of spontaneous ribosome dissociation from mRNA without producing protein

$k_b$ – rate constant of miRNA to mRNA binding

SBTOOLBOX files for Matlab containing two translation models ($M_0'$ and $M_1'$):

Model $M_0'$

********** MODEL NAME
Simple and basic model of translation $M_0$prime from Gorban et al, 2012

********** MODEL NOTES

********** MODEL STATES
\[
\frac{d}{dt}(M_0) = R_T - R_{01} - R_{M0d}
\]
\[
\frac{d}{dt}(F_0) = R_{01} - R_{02} - R_{F0d}
\]
\[
\frac{d}{dt}(M) = R_{02} - R_1 - R_{Md} + R_2
\]
\[
\frac{d}{dt}(F) = R_1 - R_2 - R_{Fd}
\]
\[
\frac{d}{dt}(R) = R_2 + R_{02} - R_3 - R_{Rd} - R_{Rrd}
\]
\[
\frac{d}{dt}(P) = R_3 - R_p
\]

$M_0(0) = 0$

$F_0(0) = 0$

$M(0) = 0$

$F(0) = 0$

$R(0) = 0$

$P(0) = 0$

********** MODEL PARAMETERS

$kt = 0.001$

$k_{01f} = 2e^{-7}$

$k_{lf} = 1e^{-2}$

$k_{02} = 6e^{-5}$
\[ k_2 = 6\times 10^{-5} \]
\[ k_3 = 0.01 \]
\[ IF_1 = 10 \]
\[ IF_2 = 10 \]
\[ S_{40} = 100 \]
\[ S_{60} = 1000 \]
\[ k_d = 1\times 10^{-5} \]
\[ k_{rd} = 0 \]
\[ k_p = 5\times 10^{-6} \]

********** MODEL VARIABLES

********** MODEL REACTIONS

\[ R_2 = k_t \]
\[ R_{01} = k_{01}\times S_{40}\times IF_1\times M_0 \]
\[ R_{02} = k_{02}\times S_{60}\times F_0 \]
\[ R_1 = k_{1f}\times S_{40}\times M \]
\[ R_2 = k_2\times S_{60}\times F \]
\[ R_3 = k_3\times R \]
\[ R_{M0d} = k_d\times M_0 \]
\[ R_{F0d} = k_d\times F_0 \]
\[ R_{Md} = k_d\times M \]
\[ R_{Fd} = k_d\times F \]
\[ R_{bd} = k_d\times R \]
\[ R_{Rkd} = k_{kd}\times R \]
\[ R_p = k_p\times P \]
\[ PR = P \]
\[ R_B = R/(M+F) \]

---

**Model M1'**

********** MODEL NAME
Simple and basic model of translation M1prime from Gorban et al, 2012

********** MODEL NOTES

********** MODEL STATES

\[ \frac{d}{dt}(M_0) = R_2 - R_{01} - R_{M0d} \]
\[ \frac{d}{dt}(M_{0IF_140S}) = R_{01} - R_{M0A} - R_{M0IF_140Sd} \]
\[ \frac{d}{dt}(F_0) = R_{M0A} - R_{02} - R_{F0d} \]
\[ \frac{d}{dt}(M) = R_{02} - R_1 - R_{Md} + R_2 \]
\[ \frac{d}{dt}(M_{IF_140S}) = R_1 - R_{MA} - R_{MIF_140Sd} \]
\[ \frac{d}{dt}(F) = R_{MA} - R_2 - R_{Fd} \]
\[ \frac{d}{dt}(R) = R_2 + R_{02} - R_3 - R_{Rkd} \]
\[ \frac{d}{dt}(P) = R_3 - R_p \]
\[ M_0(0) = 0 \]
\[ M_{0IF_140S}(0) = 0 \]
\[ F_0(0) = 0 \]
\[ M(0) = 0 \]
\[ M_{IF_140S}(0) = 0 \]
\[ F(0) = 0 \]
R(0) = 0
P(0) = 0

********** MODEL PARAMETERS
kt = 0.001
k01f = 2e-7
k01b = 2e-8
klf = 1e-2
klb = 1e-3
k02 = 6e-5
k2 = 6e-5
k3 = 0.01
ka = 0.01
IF1 = 10
IF2 = 10
S40 = 100
S60 = 1000
kd = 1e-5
krd = 0
kp = 5e-6

********** MODEL VARIABLES

********** MODEL REACTIONS

R7 = kt
R01 = k01f*S40*IF1*M0 - k01b*M0IF140S
RM0A = ka*IF2*M0IF140S
R02 = k02*S60*F0
R1 = k1f*S40*M - klb*MIF140S
RMA = ka*IF2*MIF140S
R2 = k2*S60*F
R3 = k3*R
RM0d = kd*M0
RM0IF140Sd = kd*M0IF140S
RFD0d = kd*F0
RMD = kd*M
RMIF140Sd = kd*MIF140S
RFD = kd*F
RMd = kd*M
R0rd = krd*R
Rr = kp*P
PR = P
RB = R/([M*MIF140S+F])