On the Structure of the Initiation and Elongation Rates that Maximize Protein Production in the Ribosome Flow Model

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Abstract—Translation is a crucial step in gene expression. During translation, macromolecules called ribosomes “read” the mRNA strand in a sequential manner and produce a corresponding protein. Translation is known to consume most of the cell’s energy. Maximizing the protein production rate in mRNA translation, subject to the bounded biomolecular budget, is thus an important problem in both biology and biotechnology.

We consider this problem using a mathematical model for mRNA translation called the ribosome flow model (RFM). For an mRNA strand with $n$ sites the RFM includes $n$ state-variables that encode the normalized ribosomal density at each site, and $n + 1$ positive parameters: the initiation rate and elongation rates along the chain. An affine constraint on these rates is used to model the bounded cellular budget.

We show that for a homogeneous constraint the rates that maximize the steady-state protein production rate have a special structure. They are symmetric with respect to the middle of the chain, and monotonically increase as we move towards the center of the chain. The ribosomal densities corresponding to the optimal rates monotonically decrease along the chain. We discuss some of the biological implications of these results.

Index Terms—Systems biology, synthetic biology, gene translation, maximizing protein production rate, Perron-Frobenius theory, convex optimization, eigenvalue optimization.

1 INTRODUCTION

The process in which the genetic information stored in the DNA is transformed into functional proteins is called gene expression. Two important steps in gene expression are transcription of the DNA code into messenger RNA (mRNA) by RNA polymerase, and then translation of the mRNA into proteins. During translation, macromolecules called ribosomes traverse the mRNA strand, decoding it codon by codon into a corresponding chain of amino-acids which is then folded to become a functional protein. The rate in which proteins are produced during the translation step is called the protein production rate, or the translation rate.

Translation occurs in all organisms and under almost all conditions. Understanding the various factors that affect this dynamical process has important implications to many scientific disciplines, including medicine, evolutionary biology, synthetic biology, and more.

Computational models of translation are becoming increasingly important as the amount of experimental findings related to translation increases rapidly (see, e.g., [37], [7], [11], [17], [35], [34], [6], [27], [8], [24]). Such models are particularly important in the context of synthetic biology and biotechnology, as they can provide predictions on the qualitative and quantitative effects of various manipulations of the genetic machinery on the protein production rate.

Translation is known to consume most of the cell’s energy [22], [33], [1]. Thus, it is natural to expect that evolution shaped this process so that it maximizes the protein production rate, given the limited biomolecular budget. Optimizing the translation rate is also important in biotechnology where an important objective is to maximize the translation efficiency and protein levels of heterologous genes in a new host (see, e.g., [14, Chapter 9]).

A standard model for translation-elongation is the totally asymmetric simple exclusion process (TASEP) [28], [38]. In this model particles stochastically hop along an ordered lattice of sites. Simple exclusion means that a particle cannot hop into a site that is occupied by another particle. This models hard exclusion between the particles. In the context of translation, the lattice is the mRNA strand; the particles are the ribosomes; and hard exclusion means that a ribosome cannot move forward if the codon in front of it is covered by another ribosome. TASEP is a fundamental model in non-equilibrium statistical mechanics that has been used to model numerous natural and artificial processes including traffic flow, surface growth, communication networks and more [26], [31].

The ribosome flow model (RFM) [25] is the dynamic mean-field approximation of TASEP (see, e.g., [26] section 4.9.7] and [5, p. R345]). In the RFM, mRNA molecules are coarse-grained into $n$ consecutive sites. The model includes $n$ non-linear first-order ordinary
differential equations:
\[
\begin{align*}
\dot{x}_1 &= \lambda_0 (1 - x_1) - \lambda_1 x_1 (1 - x_2), \\
\dot{x}_2 &= \lambda_1 x_1 (1 - x_2) - \lambda_2 x_2 (1 - x_3), \\
\dot{x}_3 &= \lambda_2 x_2 (1 - x_3) - \lambda_3 x_3 (1 - x_4), \\
&\vdots \\
\dot{x}_{n-1} &= \lambda_{n-2} x_{n-2} (1 - x_{n-1}) - \lambda_{n-1} x_{n-1} (1 - x_n), \\
\dot{x}_n &= \lambda_{n-1} x_{n-1} (1 - x_n) - \lambda_n x_n.
\end{align*}
\]

The state variables \(x_i(t) : \mathbb{R}_+ \to [0, 1], i = 1, \ldots, n\), describe the occupancy level of site \(i\) at time \(t\), where \(x_i(t) = 1 [x_i(t) = 0]\) indicates that site \(i\) is completely full [empty] at time \(t\). The model includes \(n + 1\) positive parameters that control the transition rate between the sites: the initiation rate into the chain, denoted \(\lambda_0\), and the elongation (or transition) rate between site \(i\) and site \(i + 1\), denoted \(\lambda_i\), \(i = 1, \ldots, n\).

The rate of ribosome flow from site \(i\) to site \(i + 1\) is \(\lambda_i x_i(t) (1 - x_{i+1}(t))\). This rate increases with \(x_i(t)\) (i.e., when site \(i\) is fuller) and decreases with \(x_{i+1}(t)\) (i.e., when the consecutive site is becoming fuller). In particular, when \(x_{i+1}(t) = 1\) (i.e., site \(i + 1\) is completely full) the rate decreases to zero. This may be interpreted as “soft exclusion”. The term \(R(t) := \lambda_n x_n(t)\) describes the rate of ribosomes exiting the mRNA chain, so \(R(t)\) is the protein production rate at time \(t\).

If we define \(x_0(t) := 1\) and \(x_{n+1}(t) := 0\) then (1) can be written more succinctly as
\[
\dot{x}_i = \lambda_{i-1} x_{i-1} (1 - x_i) - \lambda_i x_i (1 - x_{i+1}), \quad i = 1, \ldots, n.
\]

Let \(x(t, a)\) denote the solution of (1) at time \(t \geq 0\) for the initial condition \(x(0) = a\). Since the state-variables correspond to normalized occupation levels, we always assume that \(a\) belongs to the closed \(n\)-dimensional unit cube: \(C^n := \{x \in \mathbb{R}^n : x_i \in [0, 1], i = 1, \ldots, n\}\). It is straightforward to verify that this implies that \(x(t, a) \in C^n\) for all \(t \geq 0\). In other words, \(C^n\) is an invariant set of the dynamics [19].

Let \(\text{int}(C^n)\) denote the interior of \(C^n\). It was shown in [19] that the RMF is a monotone dynamical system [29] and that this implies that (1) admits a unique steady-state point \(e \in \text{int}(C^n)\). For \(x = e\) the left-hand side of all the equations in (1) is zero, so
\[
\begin{align*}
\lambda_0 (1 - e_1) &= \lambda_1 e_1 (1 - e_2), \\
\lambda_1 e_1 (1 - e_2) &= \lambda_2 e_2 (1 - e_3), \\
&\vdots \\
\lambda_{n-1} e_{n-1} (1 - e_n) &= \lambda_n e_n.
\end{align*}
\]

Denoting the steady-state translation rate by
\[
R := \lambda_n e_n
\]
yields
\[
R = \lambda_i e_i (1 - e_{i+1}), \quad i = 0, \ldots, n,
\]
where \(e_0 := 1\) and \(e_{n+1} := 0\). Thus
\[
e_{i+1} = 1 - \frac{R}{\lambda_i e_i} = \frac{R_i - R}{R_i}, \quad (6)
\]
where \(R_i := \lambda_i e_i\). Since \(e_{i+1} \in (0, 1), 0 < R < R_i\) for all \(i = 1, 2, \ldots, n - 1\). This means that the steady-state occupancy level \(e_i\) is the normalized difference between \(R_i\) and the steady-state translation rate.

Using (4), Eq. (1) becomes
\[
\begin{align*}
e_n &= R/\lambda_n, \\
e_{n-1} &= R/(\lambda_{n-1} - e_n), \\
&\vdots \\
e_2 &= R/(\lambda_2 (1 - e_3)), \\
e_1 &= R/(\lambda_1 (1 - e_2)),
\end{align*}
\]
and
\[
e_1 = 1 - R/\lambda_0.
\]

Combining (7) and (8) provides an elegant finite continued fraction [16] expression for \(R\):
\[
0 = 1 - \frac{R/\lambda_0}{1 - \frac{R/\lambda_1}{1 - \frac{R/\lambda_2}{\ldots - \frac{R/\lambda_{n-1}}{1 - R/\lambda_n}}}}
\]
Note that this equation admits several solutions for \(R\), however, we are interested only in the unique feasible solution, i.e. the solution corresponding to \(e \in \text{int}(C^n)\). Note also that (7) implies that
\[
R(c \lambda_0, \ldots, c \lambda_n) = c R(\lambda_0, \ldots, \lambda_n), \quad \text{for all } c > 0,
\]
that is, \(R\) is a homogenous function of degree one.

It is well-known that continued fractions are related to tridiagonal matrices [36], [2]. Using this, Ref. [23] provided a linear-algebraic representation of the mapping from the rates \(\lambda := [\lambda_0, \ldots, \lambda_n]\) to the steady state translation rate \(R\).

Theorem 1 [23] Given \(\lambda \in \text{int}(\mathbb{R}_+^{n+1})\), define a \((n + 2) \times (n + 2)\) symmetric irreducible Jacobi matrix \(A = A(\lambda)\) by
\[
A := \begin{bmatrix}
0 & \lambda_0^{-1/2} & 0 & 0 & \cdots & 0 & 0 \\
\lambda_0^{-1/2} & 0 & \lambda_1^{1/2} & 0 & \cdots & 0 & 0 \\
0 & \lambda_1^{1/2} & 0 & \lambda_2^{1/2} & \cdots & 0 & 0 \\
& \vdots & & & & & \\
0 & 0 & 0 & \cdots & \lambda_{n-1}^{1/2} & 0 & \lambda_n^{-1/2} \\
0 & 0 & 0 & \cdots & 0 & \lambda_n^{-1/2} & 0
\end{bmatrix}.
\]

Then the eigenvalues of \(A\) are real and distinct, and if we order them as \(\zeta_1 < \cdots < \zeta_{n+2}\) then \(\zeta_{n+2} = R^{-1/2}\).

Note that \(A\) is a (componentwise) nonnegative matrix, so \(\zeta_{n+2}\) is also the Perron root of \(A\), denoted \(\rho(A)\).
Recently, the RFM was analyzed using tools from systems and control theory. Ref. [20] has considered the RFM as a control system with input \( u(t) = \lambda_0(t) \) and output \( y(t) = R(t) \). This turns out to be a monotone control system, as defined in [4]. Ribosome recycling (see, e.g., [21] and the references therein), has been modeled by closing the loop with a positive linear feedback. It has been shown that the closed-loop system admits a unique globally asymptotically stable equilibrium point [20]. In [18], contraction theory (see, e.g., [15], [30], [3]) has been used to show that the state-variables and the control system, as defined in [4]. Ref. [20] has considered translation rate in the RFM as the following.

\[ R = R(\lambda_1, \ldots, \lambda_n) \]

The next result from [23] shows that Problem 2 (and thus Problem 1) admits several desirable properties.

1.1 Maximizing the Translation Rate

An important problem in both systems biology and biotechnology is to maximize the protein production rate, given the limited biomolecular budget. Ref. [23] formulated this in the context of the RFM as the following optimization problem.

**Problem 1** Fix the parameters \( b, w_0, w_1, \ldots, w_n > 0 \). Maximize \( R = R(\lambda_1, \ldots, \lambda_n) \), with respect to its parameters \( \lambda_1, \ldots, \lambda_n \), subject to the constraints:

\[
\begin{align*}
\sum_{i=0}^{n} w_i \lambda_i &\leq b, \\
\lambda_0, \ldots, \lambda_n &\geq 0.
\end{align*}
\]

In other words, maximize the translation rate given an affine constraint that takes into account all the rates \( \lambda_i, i = 0, \ldots, n \). This is related to factors such as the abundance of intracellular ribosomes, initiation factors, intracellular tRNA molecules, and elongation factors. For example, all tRNA molecules are transcribed by the same transcription factors (TFIIIB) and by RNA polymerase III. The values \( w_i, i = 0, \ldots, n \), can be used to provide different weighting to the different rates. It has been shown in [23] that the optimal solution always satisfies \( \sum_{i=0}^{n} w_i \lambda^*_i = b \). Of course, by scaling the \( w_i \)s we may always assume that \( b = 1 \).

By Theorem 1, Problem 1 is equivalent to the following eigenvalue minimization problem.

**Problem 2** Let \( b, w_0, w_1, \ldots, w_n > 0 \) be as in Problem 1. Consider the matrix \( A \) in (11). Minimize \( \rho(A(\lambda^*)) \) with respect to the parameters \( \lambda_0, \ldots, \lambda_n \), subject to the constraints in (12).

The two problems above are equivalent in the sense that \( \lambda^* \) is a solution of one problem if and only if it is a solution of the second. Also, for \( A^* := A(\lambda^*) \) we have \( \rho(A^*) = (R^*)^{-1/2} \).

The next result from [23] shows that Problem 2 (and thus Problem 1) admits several desirable properties.

Let \( \text{int}(\mathbb{R}_+^k) \) denote the interior of \( \mathbb{R}_+^k \) i.e. the set \{ \( x \in \mathbb{R}^k : x_i > 0, \ i = 1, \ldots, k \) \}.

**Theorem 2** [23] The solution \( \lambda^* = [\lambda_1^*, \ldots, \lambda_n^*]' \) of Problem 1 satisfies \( \lambda_i^* > 0 \) for all \( i \). Furthermore, the function \( R = R(\lambda) \) is strictly concave on \( \text{int}(\mathbb{R}_+^{n+1}) \), so Problem 1 is a convex optimization problem, and the solution \( \lambda^* \) is unique and can be found using numerical algorithms that scale well with \( n \). The optimal steady-state production rate \( R^* := R(\lambda_1^*, \ldots, \lambda_n^*) \) satisfies

\[
R^* = \frac{(\lambda_0^*)^2}{\lambda_0^* + \frac{w_1}{w_0} \lambda_1^*}.
\]

1.1.1 Maximization subject to a homogeneous constraint

It is interesting to consider the case where all the weights \( w_i \) in Problem 1 are equal. We refer to this as the homogeneous constraint case. Indeed, in this case the weights give equal preference to all the rates, so if the corresponding optimal solution satisfies \( \lambda_i^* > \lambda_j^* \) for some \( i, j \) then this implies that, in the context of maximizing \( R \), \( \lambda_i \) is “more important” than \( \lambda_j \). By (10), we may assume in this case, without loss of generality, that

\[
w_0 = \cdots = w_n = b = 1.
\]

**Example 1** Consider Problem 1 for an RFM with \( n = 7 \) and the homogenous constraint (14). Fig. 1 depicts the optimal values \( \lambda_i^*, i = 0, \ldots, 7 \), computed using a simple search algorithm (that is guaranteed to converge for convex optimization problems). It may be seen that the \( \lambda_i^* \)s are symmetric, i.e. \( \lambda_i^* = \lambda_{7-i}^* \) and that they increase towards the center of the chain. Fig. 2 depicts the corresponding optimal values \( e_i^* \). It may be seen that the steady-state occupancy levels strictly decreases along the chain.

In this paper, we analyze the properties of the optimal rates \( \lambda^* \), the corresponding steady-state occupancies \( e^* \),
and translation rate $R^*$. The next section describes our main results. Section 3 describes some of the biological implications of the theoretical results, and describes possible directions for further research. To streamline the presentation, all the proofs are placed in the Appendix.

2 MAIN RESULTS

We begin by stating several results that hold in general for Problem 1. These results are of independent interest, and will also be used to analyze the specific case of the homogeneous constraint below.

2.1 Sensitivity at the Optimal Rates

Given $\lambda^* \in \text{int}(\mathbb{R}^{n+1})$, pick $i, j \in \{0, \ldots, n\}$, with $i \neq j$, and consider the vector $\bar{\lambda}$ defined by

$$
\bar{\lambda}_k := \begin{cases} 
\lambda^*_k + \frac{\varepsilon}{w_i}, & k = i, \\
\lambda^*_k - \frac{\varepsilon}{w_j}, & k = j, \\
\lambda^*_k, & \text{otherwise},
\end{cases}
$$

where $|\varepsilon|$ is sufficiently small so that $\bar{\lambda}_k > 0$ for all $k$. Note that $\sum_{k=0}^n w_k \bar{\lambda}_k = \sum_{k=0}^n w_k \lambda^*_k = b$. Then

$$
\bar{R} := R(\bar{\lambda}) = R(\lambda^*) + \frac{\varepsilon}{w_i} \frac{\partial R(\lambda^*)}{\partial \lambda_i} - \frac{\varepsilon}{w_j} \frac{\partial R(\lambda^*)}{\partial \lambda_j} + o(\varepsilon).
$$

Using the fact that $R^* > \bar{R}$ for all $\varepsilon \in \mathbb{R} \setminus \{0\}$ (with $|\varepsilon|$ sufficiently small) implies that

$$
1 \frac{\partial R(\lambda^*)}{w_i \partial \lambda_i} = 1 \frac{\partial R(\lambda^*)}{w_j \partial \lambda_j}, \quad \text{for all } i, j.
$$

In other words, the weighted sensitivities at the optimal values are all equal. This result has already been derived in [23]. Here we give a slightly stronger result that provides a closed-form expression for the weighted sensitivities.

**Proposition 1** Consider Problem 1. The weighted sensitivities at the optimal parameter values satisfy

$$
\frac{1}{w_i} \frac{\partial}{\partial \lambda_i} R(\lambda^*) = \frac{R(\lambda^*)}{b}, \quad i = 0, \ldots, n.
$$

**Remark 1** For the case of a homogeneous constraint, this yields $\frac{\partial}{\partial \lambda_i} R(\lambda^*) = R(\lambda^*)/b$, $i = 0, \ldots, n$, so in particular all the sensitivities at the optimal solution are equal. This is reasonable, as otherwise it would be possible to find a better solution by placing a larger [smaller] rate $\lambda_i$ at site $i$ [j] that has a higher [lower] sensitivity, while preserving the total bound on the rates. This also implies that to first-order in $\varepsilon$,

$$
R(\lambda^* + \varepsilon e^k) = R(\lambda^*) + \varepsilon \frac{\partial}{\partial \lambda_k} R(\lambda^*) = R(\lambda^*) + \varepsilon R(\lambda^*),
$$

where $e^k$ is the vector with 1 in entry $k$, and 0 elsewhere.

Note that Prop. 1 implies that the optimal solution of Problem 2 satisfies

$$
\frac{1}{w_i} \frac{\partial}{\partial \lambda_i} R(A^*) = -\frac{1}{2b} \rho(A^*), \quad i = 0, \ldots, n.
$$

**Example 2** Consider the very simple case of an RFM with $n = 1$. Solving (9) yields $R = \frac{w_0 \lambda_0 + w_1 \lambda_1}{w_1 (w_1 - w_0) \lambda_0 + b}$. The unique maximizing value is $\lambda^*_0 = \frac{b}{w_0 + \sqrt{w_0 w_1}}$, so $\lambda^*_1 = \frac{b}{w_1 + \sqrt{w_0 w_1}}$, and

$$
R^* = R(\lambda^*_0, \lambda^*_1) = \frac{b}{(\sqrt{w_0} + \sqrt{w_1})^2}.
$$

On the other-hand, the derivatives are

$$
\frac{\partial R}{\partial \lambda_0} = \frac{\lambda_1^2}{(\lambda_0 + \lambda_1)^2}, \quad \frac{\partial R}{\partial \lambda_1} = \frac{\lambda_0^2}{(\lambda_0 + \lambda_1)^2},
$$

and substituting the optimal values yields $\frac{\partial R(\lambda^*)}{\partial \lambda_i} = \frac{\lambda_i^*}{w_i R^*/b}$, $i = 0, 1$.

2.2 Optimal Steady-State Occupancies

Let $c_i^* = c_i(\lambda^*_0, \ldots, \lambda^*_n)$ denote the steady-state occupancy levels corresponding to the optimal rates. Our first result relates these occupancy levels to the optimal rates.

**Proposition 2** The steady-state occupancy levels corresponding to the optimal rates satisfy

$$
\frac{\lambda_{i+1}^*}{\lambda_i^*} = \frac{w_i}{w_{i+1}} \frac{c_{i+1}^*}{1 - c_{i+1}^*}, \quad i = 0, \ldots, n - 1.
$$

Prop. 2 implies that given the optimal rates $\lambda_i^*$ the corresponding steady-state occupancies can be determined via

$$
c_{i+1}^* = \left(1 + \frac{\lambda_i^*}{\lambda_{i+1}^*} \frac{w_i}{w_{i+1}}\right)^{-1},
$$

**Fig. 2.** $c_i^*$ as a function of $i$ for an RFM with $n = 7$ and the homogenous constraint (14).
instead of by solving (3).

The \( e_i^* \)'s thus satisfy two sets of equations: the set given in Prop. 2 and the set based on the RFM steady-state equation (3), that is,

\[
e_i^* = \frac{\lambda_{i+1}^* e_{i+1}^*}{1 - e_{i+1}^*} (1 - e_{i+2}^*), \quad i = 0, \ldots, n - 1.
\]

Combining these sets of equations yields the following.

**Corollary 1** The optimal occupancies satisfy

\[
e_i^* = \frac{w_i}{w_{i+1}} \left( \frac{e_{i+1}^*}{1 - e_{i+1}^*} \right)^2 (1 - e_{i+2}^*), \quad i = 0, \ldots, n - 1, \tag{20}
\]

with \( e_0^* := 1 \) and \( e_{n+1}^* := 0 \).

**Example 3** Consider Problem II for an RFM with \( n = 3 \) and the homogeneous constraint (14). In this case, (20) yields

\[
1 = \left( \frac{e_1^*}{1 - e_1^*} \right)^2 (1 - e_2^*),
\]

\[
e_1^* = \left( \frac{e_2^*}{1 - e_2^*} \right)^2 (1 - e_3^*),
\]

\[
e_2^* = \left( \frac{e_3^*}{1 - e_3^*} \right)^2.
\]

Solving this yields

\[
e^* = \left[ 2 - \sqrt{3}, 1/2, \sqrt{2} - 1 \right]^T. \tag{21}
\]

Now applying (18) and using the fact that \( \lambda_0^* + \cdots + \lambda_n^* = 1 \), yields

\[
\lambda^* = \left[ 2\sqrt{3} - 1, \sqrt{3} - 2, -\sqrt{2}, -2\sqrt{2} + 1 \right]^T. \tag{22}
\]

**Remark 2** An important question is how many \( \lambda_i^* \) values are needed in order to uniquely determine \( R^* \)? It follows from (13) that knowing \( \lambda^*_0 \) and \( \lambda^*_1 \) is enough. Also, it follows from (19) with \( i = n - 1 \) that

\[
R^* = \lambda_n^* e_n^* = \frac{(\lambda_n^*)^2}{\lambda_n^* + \frac{w_{n-1}}{w_n} \lambda_{n-1}^*}.
\]

Thus, knowing either the first or the last two optimal rates is enough to uniquely determine \( R^* \).

### 2.3 Homogeneous Constraint

As noted above, it is interesting to consider Problem I with the homogeneous constraint (14). The following result proves that in this case the optimal solution \( \lambda^* \) and the corresponding \( e^* \) always have the structure depicted in Figs. 1 and 2.

**Proposition 3** Consider Problem I with the homogeneous constraint (14). Then the following properties hold.

- The optimal rates satisfy \( \lambda_0^* < \lambda_1^* < \cdots < \lambda_{n-1}^* \) and
  \[
  \lambda_i^* = \lambda_{n-i}^*, \quad i = 0, \ldots, n. \tag{23}
  \]
- The corresponding steady-state occupancies satisfy
  \[
  e_i^* = 1 - e_{n-i+1}^*, \quad i = 1, \ldots, n. \tag{24}
  \]

If \( n \) is even then

\[
e_1^* > \cdots > e_{n-1}^* > \frac{1}{2} > e_{n+1}^* > \cdots > e_n^*, \tag{25}
\]

and if \( n \) is odd then

\[
e_1^* > \cdots > e_{n-1}^* > e_{n+1}^* = \frac{1}{2} > e_{n+2}^* > \cdots > e_n^*. \tag{26}
\]

Note that (24) implies that \( \sum_{i=1}^n e_i^* = n/2 \). Note also that the results in (21) and (22) agree of course with the results in Prop. 3.

### 3 Discussion

Gene translation is known to be one of the most energy consuming processes in the cell. Thus, it is reasonable to assume that this process evolved such that the protein production rate of highly-expressed genes is optimized given the limited cell resources. Maximizing the translation rate is also important in gene cloning for biotechnological applications.

The RFM is a deterministic mathematical model for translation-elongation obtained via a mean-field approximation of a fundamental model from non-equilibrium statistical mechanics called TASEP. The RFM includes \( n + 1 \) positive parameters: the initiation rate \( \lambda_0 \), and the elongation rates \( \lambda_1, \ldots, \lambda_n \).

It is possible to formulate the problem of optimizing the steady-state translation rate \( R \), subject to the limited biomolecular budget, as a constrained optimization problem using the RFM. This problem has several desirable properties that follow from the fact that \( R \) is a strictly concave function of the rates \( \lambda_i, i = 0, \ldots, n \) [23].

In this paper, we analyzed the optimal vector of initiation and elongation rates \( \lambda^* \), and the corresponding steady-state occupancies (ribosomal densities) \( e^* \). Our results show that for a constraint that gives equal weighting to all the rates, \( \lambda^* \) has a special structure: the rates \( \lambda_i^* \) are symmetric with respect to the center of the chain, and strictly decrease as we move towards the ends of the chain. This holds for every dimension \( n \). The reason for this structure is the particle-hole symmetry, and the fact that sites at the center of the chain have a large number of neighboring sites. These results agree with the so called “edge-effect” in TASEP (see, for example, [10] and [9]), i.e. the fact that the output rate is less sensitive to the rates close to the edges of the chain.

Since the optimal rates close to the two ends of the chain are relatively small, these rates may be considered as the limiting factors of the translation process. Yet, this intuitive interpretation is wrong. Indeed, at the optimal
solution all the sensitivities to a change in any of the rates are equal (see Remark 1), so all the rates limit the translation rate to the same extent. The rates towards the center of the chain have a higher effect on \( R \) and, therefore, the optimal solution includes lower rates at the ends of the chain. An important open problem in gene translation is what is the dominant gene translation regime: some studies claim that initiation is the rate limiting step \([12]\), while others claim that the elongation step is also rate limiting \([32], [33]\). Our results suggest that in addressing this question one must take into account not only the values of the initiation and elongation rates, but also the sensitivity of the production rate with respect to these rates.

An interesting topic for further research is maximizing the protein production rate when some of the rates are fixed. For example, suppose that we fix one or more of the rates to small values so that they form a bottleneck in the chain. Then optimizing over the other rates provides information on how to overcome the decrease due to the bottlenecks in an optimal manner. For example, consider the RFM with the bottlenecks in an optimal manner. For example, our results suggest that in regime: some studies claim that initiation is the rate limiting \([32], [33]\). Our results suggest that in

\[
\tilde{\lambda} = [0.0935, 0.3965, 0.02, 0.3965, 0.0935]',
\]

and \( \tilde{R} = 0.0178 \). Comparing this to (27), we see that \( \tilde{\lambda}_i > \lambda_i^* \), \( i = 1, 3 \). Indeed, these rates must increase in order to compensate for the forced slow rate at site 2. Note that although \( \tilde{\lambda}_2/\lambda_2^* = 0.083 \), \( \tilde{R}/R^* = 0.2786 \). Thus, the optimal solution is able to compensate to some extent, for the drastic reduction in the elongation rate.

Fig. 3 depicts the occupancy levels \( \tilde{e}_i \), \( i = 1, \ldots, 4 \), corresponding to \( \tilde{\lambda} \). Now of course the properties in Prop. 3 no longer hold. As expected, forcing \( \lambda_2 \) to a low value yields a high [low] value for \( \tilde{e}_2 [\tilde{e}_3] \).

\[\text{APPENDIX: PROOFS}\]

\textbf{Proof of Prop. 1} By Euler’s theorem for homogeneous functions, \[
R(\lambda) = \sum_{i=0}^{n} \lambda_i \frac{\partial R(\lambda)}{\partial \lambda_i} = \sum_{i=0}^{n} \lambda_i w_i \left( 1 \frac{\partial R(\lambda)}{\partial \lambda_i} \right).
\]

Substituting \( \lambda = \lambda^* \) and using (15) yields

\[
R(\lambda^*) = \frac{1}{w_i} \frac{\partial R(\lambda^*)}{\partial \lambda_i} = \frac{1}{w_i} \frac{\partial R(\lambda^*)}{\partial \lambda_i} \sum_{i=0}^{n} \lambda_i w_i = \frac{1}{w_i} \frac{\partial R(\lambda^*)}{\partial \lambda_i} b_i,
\]

and this completes the proof of Prop. 1.

\textbf{Proof of Prop. 2} For \( \lambda \in \text{int}(\mathbb{R}_+^{n+1}) \) and \( i \in \{0, \ldots, n\} \), define

\[
G_{n-i}(z) := 1 - \frac{z/\lambda_i}{1 - \sum_{j=0}^{i-1} \lambda_j w_j}.
\]

Note that (29) implies that

\[
G_n(R(\lambda)) = 0, \quad \text{for all } \lambda \in \text{int}(\mathbb{R}_+^{n+1}),
\]

and that (7) and (8) yield

\[
G_{n-i}(R(\lambda)) = 1 - e_i(\lambda),
\]

for all \( \lambda \in \text{int}(\mathbb{R}_+^{n+1}), \ i = 0, \ldots, n \).

We require the following result.

\textbf{Proposition 4} For all \( i = 0, \ldots, n \),

\[
\frac{\partial G_n}{\partial \lambda_i}(z) = \frac{z^{i+1}}{(\prod_{\ell=0}^{i-1} \lambda_{\ell}) (\prod_{\ell=1}^{i} G_{n-\ell}(z)) \lambda_i^2 G_{n-(i+1)}(z)}.
\]

\textbf{Proof of Prop. 4} Pick \( k \in \{0, 1, \ldots, n - 1\} \). By (28), \( G_{n-k}(z) = 1 - e_k(\lambda) \). Therefore,

\[
\frac{\partial G_{n-k}}{\partial \lambda_j} = \frac{z}{\lambda_k G_{n-(k+1)}^2} \frac{\partial G_{n-(k+1)}}{\partial \lambda_j}, \quad \text{for all } j \neq k,
\]

for \( z \in (0,1) \), \( \lambda \in (0,1) \), and \( G \) is continuous on \((0,1) \times (0,1) \times (0,1) \).
and

\[
\frac{\partial G_{n-k}}{\partial \lambda_k} = \frac{z}{\lambda_k^2 G_{n-(k+1)}}.
\]

(32)

Thus,

\[
\frac{\partial G_n}{\partial \lambda_i} = \frac{z}{\lambda_0^2 G_{n-1}} \frac{\partial G_{n-1}}{\partial \lambda_i} = \frac{z}{\lambda_0 G_{n-1}} \lambda_1^2 G_{n-2} \frac{\partial G_{n-2}}{\partial \lambda_i} \ldots = \frac{z^i}{(\prod_{k=0}^{n-1} \lambda_k)} \frac{\partial G_{n-i}}{\partial \lambda_i},
\]

and using (32) completes the proof of Prop. 3.

Fact 1 In the TASEP literature, this is known as the particle-hole symmetry (see, e.g., [13]).

Note that (34) implies in particular that

\[
R = \zeta_n e_n = \lambda_0 (1 - \epsilon_1) = \bar{R},
\]

where the last step follows from (5). Thus,

\[
R(\zeta_0, \zeta_1, \ldots, \zeta_n) = R(\zeta_n, \zeta_{n-1}, \ldots, \zeta_0).
\]

(35)

Let \( \lambda^* \) denote the optimal solution for Problem 1 with the homogeneous constraint. Since \( w_i = \infty \) for all \( i = 0, \ldots, \lceil n/2 \rceil \), the vector \( \lambda^* := [\lambda_n^*, \lambda_{n-1}^*, \ldots, \lambda_0^*] \) satisfies the constraint \( \sum_{i=0}^{n} w_i \lambda_i^* = b \). By (35), \( \lambda^* \) is also an optimal solution. By uniqueness of the optimal solution, \( \lambda_n^* = \lambda^* \). This proves (23), and using Fact 1 proves (24).

To prove that the \( \lambda_i^* \)'s increase as we move towards the center of the chain, note that by (15),

\[
\frac{\lambda_n^*}{\lambda_0^*} = \frac{e_1^*}{1 - e_1^*}.
\]

(36)

On the other-hand (3) gives \( \frac{\lambda_i^*}{\lambda_j^*} = \frac{1 - e_i^*}{1 - e_j^*} \), so

\[
\left( \frac{\lambda_i^*}{\lambda_j^*} \right)^2 = \frac{1}{1 - e_i^*}.
\]

(37)

and (36) implies that

\[
e_1^* > 1/2.
\]

(38)

Consider first the case where \( n \) is even. Let \( m := n/2 \). We need to show that

\[
\lambda_0^* < \lambda_1^* < \cdots < \lambda_m^*.
\]

(39)

Seeking a contradiction, assume that

\[
\lambda_{m-1}^* \geq \lambda_m^*.
\]

(40)

Then (18) gives \( e_m^* \leq 1/2 \). Now (3) and (24) yield

\[
e_{m-1}^* = \lambda_m^* e_m^* (1 - e_{m+1}^*) \leq 1 \times 1 \times e_{m-m}^* = e_m^*,
\]

so \( e_{m-1}^* \leq 1/2 \). Combining this with (18) yields \( \lambda_{m-2}^* \geq \lambda_{m-1}^* \). Now (3) and (24) yield

\[
e_m^{m-2} = \frac{\lambda_{m-2}^*}{\lambda_{m-2}^* - 1 - e_{m-1}^*} \leq e_m^*,
\]

so \( e_{m-2}^* \leq 1/2 \). Proceeding in this way yields \( \lambda_m^* \leq \lambda_{m-1}^* \leq \cdots \leq \lambda_1^* \leq \lambda_0^* \). This contradicts (37), and thus...
proves that
\[ \lambda^*_m - \lambda^*_m \leq 0. \]

We can now prove, in a similar fashion, that \( \lambda^*_{m-2} < \lambda^*_m \) and then that \( \lambda^*_{m-3} < \lambda^*_m \), etc., and this yields (39). Applying Prop. 2 yields \( \epsilon^*_m > 1/2 \), \( i = 1, \ldots, m \). Combining this with (39), (7), and (24) proves (26).

We now turn to the case where \( n \) is odd. Let \( m := (n - 1)/2 \). Note that (24) implies that \( e^*_m + 1 = 2/m \). We need to show that (39) holds. Seeking a contradiction, assume that
\[ \lambda^*_{m-1} \geq \lambda^*_m. \]

Then (18) gives \( e^*_m \leq 1/2 \). Now (5) and (26) yield
\[ e^*_m = \frac{\lambda^*_m - e^*_m}{\lambda^*_{m-1} - e^*_m} (1 - e^*_{m+1}) \leq 1 \times 1 \times 1/2. \]

Combining this with (18) yields \( \lambda^*_{m-2} \geq \lambda^*_m \). Proceeding as above yields \( \lambda^*_{m-3} \leq \lambda^*_{m-1} \), etc., \( \lambda^*_{m-1} \leq \lambda^*_{m-1} \), etc. This contradicts (37), and thus proves that
\[ \lambda^*_{m-1} < \lambda^*_m. \]

We can now prove, in a similar fashion, that \( \lambda^*_{m-2} < \lambda^*_m \) and then that \( \lambda^*_{m-3} < \lambda^*_m \), etc., and this yields (29). The proof of (26) follows as in the case where \( n \) is even. This completes the proof of Prop. 3.

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