Technical Report
Limitations and Trade-offs in Gene Expression due to Competition for Shared Cellular Resources

Andras Gyorgy and Domitilla Del Vecchio

This is a technical report accompanying the paper entitled "Limitations and trade-offs in gene expression due to competition for shared cellular resources" [1]. Here, we first introduce the conservation laws for RNAP and ribosomes, then show that instead of input concentrations, we can focus on the activation level of genes. This is followed by the characterization of the approximate realizable region $\mathcal{S}$, then we show that the realizable region $\mathcal{P}$ lies inside $\mathcal{S}$. Finally, we present the typical range of biochemical parameters considered in [1].

I. LIMITED AVAILABILITY OF SHARED RESOURCES

According to [2], RNAP can be divided into four main categories when exogenous proteins p_i are not expressed: immature RNAP, free RNAP, and RNAP bound specifically (and transcribing) and non-specifically to the chromosome. Based on [3], the cell has approximately 1500 RNAP molecules ($x_T = 1500$nM), among which about 200 are actively transcribing endogenous genes ($x_S = 200$nM) at low growth rate. Furthermore, [2] suggests that the ratio of immature RNAP is negligible, and the remaining 1300 molecules are partitioned as follows: 100 of them are free ($x = 100$nM), whereas 1200 are non-specifically bound ($x_N = 1200$nM). Furthermore, let $x_U = \sum_{i=1}^{n} c_i$ denote the RNAP usage of exogenous proteins p_i for $i = 1, 2, \ldots, n$, yielding the conservation law

$$x_T = x + x_S + x_N + x_U. \tag{S1}$$

As for ribosomes, [3] reports that the number of ribosomes per cell is 6800 ($y_T = 6800$nM), 80% of which is active, that is, approximately 5500 ($y_S = 5500$nM) at low growth rate. According to [4], the concentration of free ribosomes is approximately 15%, so that the ratio of non-specifically bound ribosomes and immature ribosomes is about 5%. This is negligible compared to the fraction of active and free ribosomes, unlike in the case of RNAP. For simplicity, we treat this last 5% as if they belonged to the pool of free ribosomes (so that we slightly under-estimate the effect of competition for ribosomes). Moreover, let $y_U = \sum_{i=1}^{n} d_i$ denote the ribosome usage of exogenous proteins p_i for $i = 1, 2, \ldots, n$, which yields

$$y_T = y + y_S + y_U. \tag{S2}$$

When exogenous proteins p_i are not expressed, the proteome can be divided into three classes [5]. The Q-class of mass fraction ϕ_Q represents a fixed core sector, the R-class of mass fraction ϕ_R contains all the ribosomal proteins and their affiliates, and the P-class of mass fraction ϕ_P represents the remaining proteins [5]. Upon expression of exogenous proteins the corresponding U-class of mass fraction ϕ_U is introduced, yielding $\phi_U = 1-(\phi_Q+\phi_R+\phi_P)$ [5]. Since the growth rate is a linear function of ϕ_P and an affine function of ϕ_R, this implies that ϕ_P and ϕ_R remain constant if the growth rate does not change [5]. This together with the fact that ϕ_Q represents a core fixed sector by definition implies that $\phi_U = 1 - (\phi_Q + \phi_R + \phi_P)$ is also constant.

In the conservation laws (S1)–(S2), the RNAP and ribosome usage of the P, Q and R class proteins are represented by x_S and y_S, respectively. Since ϕ_P, ϕ_Q and ϕ_R remain constant upon expression of exogenous proteins, we first conclude that both x_S and y_S remain unaffected. Second, we assume that the synthesized cellular machinery by these classes remain constant, so that x_T and y_T are also unaffected by the expression of exogenous proteins. As a result, with $X = x_T - x_S$ and $Y = y_T - y_S$ we obtain that X and Y are constant. Furthermore, we approximate the concentration x_N of the weak non-specific binding of RNAP to the DNA as $x_N = W_x x$ with $W_x > 0$, so that (S1)–(S2) yield

$$X = (1 + W_x)x + \sum_{i=1}^{n} \epsilon_i \eta_i \frac{x}{x + \kappa_i}, \tag{S3}$$

$$Y = y + \sum_{i=1}^{n} \epsilon_i \frac{\gamma_i \eta_i}{\delta_i} \frac{x}{x + \kappa_i} \frac{y}{y + k_i}. \tag{S4}$$

II. ACTIVATION LEVEL OF GENES

It is shown in [1] that the concentration of p_i is given by

$$p_i = \epsilon_i \frac{\pi_i}{\lambda_i} \frac{\gamma_i \eta_i}{\delta_i} \frac{x}{x + \kappa_i} \frac{y}{y + k_i} \tag{S5}$$

for $i = 1, 2, \ldots, n$, where x and y satisfy the constraints (S3)–(S4) with

$$\epsilon_i = \frac{\frac{u_i}{\mu_i}\left(1 + \frac{x}{\kappa_i}\right)}{1 + \frac{u_i}{\mu_i}\left(1 + \frac{x}{\kappa_i}\right)}, \qquad \text{for } i = 1, 2, \ldots, n. \tag{S6}$$

This work was supported by AFOSR grant FA9550-12-1-0129 and NIGMS grant P50 GM098792.

A. Gyorgy is with the Department of Electrical Engineering and Computer Science, MIT, Cambridge, MA 02139, USA gyorgy@mit.edu

D. Del Vecchio is with the Department of Mechanical Engineering, MIT, Cambridge, MA 02139, USA ddv@mit.edu

Referring to [1], we rewrite (S6) as

$$\epsilon = E(u, x), \tag{S7}$$

and (S3)–(S4) as

$$X = F_\epsilon(\epsilon, x) \qquad \text{and} \qquad Y = G_\epsilon(\epsilon, x, y), \tag{S8}$$

respectively, and (S5) with $p = (p_1, p_2, \ldots, p_n)^T$ as

$$p = H_\epsilon(\epsilon, x, y). \tag{S9}$$

Furthermore, we introduce

$$\begin{aligned} F(u, x) =& F_\epsilon(E(u, x), x), \\ G(u, x, y) =& G_\epsilon(E(u, x), x, y), \\ H(u, x, y) =& H_\epsilon(E(u, x), x, y), \end{aligned} \tag{S10}$$

and the sets $\mathcal{U} = [0, \infty)^n$ and

$$\begin{aligned} \mathcal{P} = \{p \mid p = H(u, x, y),\ X = F(u, x),\ Y = G(u, x, y), \\ x \in [0, X],\ y \in [0, Y],\ u \in \mathcal{U}\}. \end{aligned} \tag{S11}$$

In what follows, we show that in order to find the realizable region $\mathcal{P}$, it is sufficient to consider (S3)–(S5) for $\epsilon \in \mathcal{E} = [0, 1)^n$, instead of considering (S3)–(S5) with (S6) for $u \in \mathcal{U}$.

Claim 1. *Take $F(u, x)$ and $G(u, x, y)$ defined in* (S10)*. For $u \in \mathcal{U}$, there is a unique $(x, y) \in [0, X] \times [0, Y]$ such that $F(u, x) = X$ and $G(u, x, y) = Y$. As a result, there exist functions $f, g : \mathbb{R}^n \to \mathbb{R}$ such that $x = f(u)$ and $y = g(u)$.*

Proof: According to (S10), we have

$$F(u, x) = (1 + W_x)x + \sum_{i=1}^{n} \frac{\frac{u_i}{\mu_i}\left(1 + \frac{x}{\kappa_i}\right)\frac{\eta_i x}{x + \kappa_i}}{1 + \frac{u_i}{\mu_i}\left(1 + \frac{x}{\kappa_i}\right)} - X. \tag{S12}$$

Fix $u \in \mathcal{U}$. Since $F(u, x)$ is continuous and $F(u, 0) = 0$ and $F(u, X) > X$ by (S12), there is at least one $x \in [0, X]$ such that $F(u, x) = X$, according to the Intermediate Value Theorem [6]. Furthermore, since $F(u, x)$ in (S12) is strictly increasing with x, there is exactly one $x \in [0, X]$ such that $F(u, x) = X$. Then, let $f : \mathbb{R}^n \to \mathbb{R}$ be the function that maps u to this unique x, that is, $F(u, f(u)) = X$. The proof for G can be constructed similarly. ∎

With $H(u, x, y)$ defined in (S10), introduce $A : \mathbb{R}^n \to \mathbb{R}^n$ as $A(u) = H(u, f(u), g(u))$, so that (S11) can be written as

$$\mathcal{P} = \{p \mid p = A(u),\ u \in \mathcal{U}\}. \tag{S13}$$

Claim 2. *Take $F_\epsilon(\epsilon, x)$ and $G_\epsilon(\epsilon, x, y)$ from* (S8)*. For $\epsilon \in \mathcal{E}$, there is a unique $(x, y) \in [0, X] \times [0, Y]$ such that $F_\epsilon(\epsilon, x) = X$ and $G_\epsilon(\epsilon, x, y) = Y$. As a result, there exist functions $f_\epsilon, g_\epsilon : \mathbb{R}^n \to \mathbb{R}$ such that $x = f_\epsilon(\epsilon)$ and $y = g_\epsilon(\epsilon)$.*

Proof: Similar to the proof of Claim 1. ∎

Claim 3. *Take $u \in \mathcal{U}$, the functions f and g defined in Claim 1, together with f_ϵ and g_ϵ defined in Claim 2. Furthermore, consider $\epsilon = E(u, f(u))$ from* (S7) *with $x = f(u)$. Then $f(u) = f_\epsilon(\epsilon)$ and $g(u) = g_\epsilon(\epsilon)$.*

Proof: By Claim 1, we have $X = F(u, (f(u)))$, yielding $X = F(u, (f(u))) = F_\epsilon(E(u, f(u)), f(u))$ from (S10), and since $\epsilon = E(u, f(u))$ by assumption, we obtain $X = F_\epsilon(\epsilon, f(u))$. We further have $X = F_\epsilon(\epsilon, f_\epsilon(\epsilon))$ by Claim 2. As a result, we obtain that $x = f(u)$ and $x = f_\epsilon(\epsilon)$ are both solutions of $X = F_\epsilon(\epsilon, x)$, and since it has a unique solution by Claim 2, we conclude that $f(u) = f_\epsilon(\epsilon)$. The proof of $g(u) = g_\epsilon(\epsilon)$ can be constructed similarly. ∎

With $H_\epsilon(\epsilon, x, y)$ defined in (S9), introduce the function $A_\epsilon : \mathbb{R}^n \to \mathbb{R}^n$ as $A_\epsilon(\epsilon) = H_\epsilon(\epsilon, f_\epsilon(\epsilon), g_\epsilon(\epsilon))$ and the set

$$\mathcal{P}_\epsilon = \{p \mid p = A_\epsilon(\epsilon),\ \epsilon \in \mathcal{E}\}. \tag{S14}$$

Lemma 1. *With $\mathcal{P}$ and $\mathcal{P}_\epsilon$ given in* (S13) *and* (S14)*, respectively, we obtain that $\mathcal{P} = \mathcal{P}_\epsilon$.*

Proof: Let $x = f(u)$ and $y = g(u)$ denote the unique solutions of $F(u, x) = X$ and $G(u, x, y) = Y$ with $(x, y) \in [0, X] \times [0, Y]$ for $u \in \mathcal{U}$, respectively (Claim 1). Referring to (S8), let $x = f_\epsilon(\epsilon)$ and $y = g_\epsilon(\epsilon)$ denote the unique solutions of $F_\epsilon(\epsilon, x) = X$ and $G_\epsilon(\epsilon, x, y) = Y$ with $(x, y) \in [0, X] \times [0, Y]$ for $\epsilon \in \mathcal{E}$, respectively (Claim 2).

To prove that $\mathcal{P} \subseteq \mathcal{P}_\epsilon$ we show that for every $u \in \mathcal{U}$ there is an $\epsilon \in \mathcal{E}$ such that $A(u) = A_\epsilon(\epsilon)$. First, consider $\epsilon = E(u, f(u))$, and given that $f(u) \in [0, X]$, we conclude that $\epsilon_i \in [0, 1)$ by (S6), so that $\epsilon \in \mathcal{E}$ by the definition of $\mathcal{E}$. Second, considering (S10) implies $A(u) = H(u, f(u), g(u)) = H_\epsilon(E(u, f(u)), f(u), g(u))$, so that $\epsilon = E(u, f(u))$ together with $f(u) = f_\epsilon(\epsilon)$ and $g(u) = g_\epsilon(\epsilon)$ from Claim 3 yield $A(u) = H_\epsilon(\epsilon, f_\epsilon(\epsilon), g_\epsilon(\epsilon)) = A_\epsilon(\epsilon)$, where we used the definition of $A_\epsilon(\epsilon)$.

Similarly, to show that $\mathcal{P}_\epsilon \subseteq \mathcal{P}$ it is sufficient to prove that for every $\epsilon \in \mathcal{E}$ there is a $u \in \mathcal{U}$ such that $A(u) = A_\epsilon(\epsilon)$. Since (S6) yields $u_i = \epsilon_i \mu_i \kappa_i / [(1 - \epsilon_i)(\kappa_i + f_\epsilon(\epsilon))]$, and given that $\epsilon_i \in [0, 1)$ as $\epsilon \in \mathcal{E}$, we obtain $u_i \in [0, \infty)$, so that $u \in \mathcal{U}$.

The part $A(u) = A_\epsilon(\epsilon)$ can be showed similarly. ∎

III. APPROXIMATE REALIZABLE REGION

Referring to [1], using the approximations $x \ll \kappa_i$ and $y \ll k_i$ for $i = 1, 2, \ldots, n$, we obtain that (S5) can be written as

$$p_i = \frac{Q_i \epsilon_i}{1 + \sum_{i=1}^{n} R_i \epsilon_i}, \qquad \text{for } i = 1, 2, \ldots, n \tag{S15}$$

with

$$\begin{aligned} Q_i =& \frac{1}{1 + W_x} \frac{\pi_i}{\lambda_i} \frac{\gamma_i \eta_i}{\delta_i} \frac{1}{\kappa_i k_i} XY, \\ R_i =& \frac{1}{1 + W_x} \left(\frac{\gamma_i \eta_i}{\delta_i} \frac{1}{\kappa_i k_i} X + \frac{\eta_i}{\kappa_i} \right). \end{aligned} \tag{S16}$$

Furthermore, let $\hat{A} : \mathbb{R}^n \to \mathbb{R}^n$ be the function mapping ϵ to p according to (S15), so that $p = \hat{A}(\epsilon)$. Next, define

$$p_i^{\max} = \frac{Q_i}{1 + R_i} \qquad \text{and} \qquad p_i^{\infty} = \frac{Q_i}{R_i}, \tag{S17}$$

and introduce the simplex $\mathcal{S}_i$ for $i = 1, 2, \ldots, n$ as

$$\mathcal{S}_i = \left\{ p \mid p \geq 0 \text{ and } \frac{p_i}{p_i^{\max}} + \sum_{\substack{j=1 \\ j \neq i}}^{n} \frac{p_j}{p_j^{\infty}} < 1 \right\}. \tag{S18}$$

Lemma 2. *Let*

$$\mathcal{S} = \{p \mid p = \hat{A}(\epsilon),\ \epsilon \in \mathcal{E}\}. \tag{S19}$$

Then, we obtain $\mathcal{S} = \cap_{i=1}^{n} \mathcal{S}_i$ *where* $\mathcal{S}_i$ *is defined in* (S18).

Proof: We first show $\mathcal{S} \subseteq \cap_{i=1}^{n} \mathcal{S}_i$ as follows. Introduce $\mathcal{E}_i = \{\epsilon \mid \epsilon_i \in [0,1) \text{ and } \epsilon_j \in [0,\infty) \text{ for } j \neq i\}$ and let $P_i = Q_i\epsilon_i/(1 + W_x + R_i\epsilon_i)$, so that we have $P_i < p_i^{\max}$ by (S17). Furthermore, $p = \hat{A}(\epsilon)$ satisfies

$$\frac{p_i}{P_i} + \sum_{\substack{j=1 \\ j\neq i}}^{n} \frac{p_j}{p_j^{\infty}} = 1 \tag{S20}$$

by substitution of (S15) into (S20). The fact that $\epsilon \in \mathcal{E}$ yields $p \geq 0$ by (S15), and $P_i < p_i^{\max}$ with (S20) result in

$$\frac{p_i}{p_i^{\max}} + \sum_{\substack{j=1 \\ j\neq i}}^{n} \frac{p_j}{p_j^{\infty}} < \frac{p_i}{P_i} + \sum_{\substack{j=1 \\ j\neq i}}^{n} \frac{p_j}{p_j^{\infty}} = 1,$$

so that $p \in \mathcal{S}_i$ by (S18) for $\epsilon \in \mathcal{E}_i$. Combining this together with the fact that $\epsilon \in \mathcal{E} = \cap_{i=1}^{n} \mathcal{E}_i$ yields that $\mathcal{S} \subseteq \cap_{i=1}^{n} \mathcal{S}_i$.

Second, we prove $\cap_{i=1}^{n} \mathcal{S}_i \subseteq \mathcal{S}$ by showing that for any $p \in \cap_{i=1}^{n} \mathcal{S}_i$ there exists an $\epsilon \in \mathcal{E}$ such that $p = \hat{A}(\epsilon)$. To this end, pick $p \in \cap_{i=1}^{n} \mathcal{S}_i$ and define

$$P_i = \frac{p_i}{1 - \sum_{\substack{j=1 \\ j\neq i}}^{n} \frac{p_j}{p_j^{\infty}}} \qquad \text{and} \qquad \epsilon_i = \frac{P_i}{Q_i - R_i P_i} \tag{S21}$$

for $i = 1, 2, \ldots, n$. Substituting ϵ into (S15) we obtain that $p = \hat{A}(\epsilon)$. Therefore, it is only left to show that $\epsilon \in \mathcal{E}$. Given that $p \in \cap_{i=1}^{n} \mathcal{S}_i$, we obtain by (S18) that $0 \leq p_i < p_i^{\max}$ and $0 \leq \sum_{j=1, j\neq i}^{n} p_j/p_j^{\infty} < 1$. Combining this together with (S21) yields that $P_i \in [0, p_i^{\max})$. Having $P_i = 0$ and $P_i = p_i^{\max}$ result in $\epsilon_i = 0$ and $\epsilon_i = 1$ in (S21) by (S17). Furthermore, as ϵ_i in (S21) is a strictly increasing function of P_i for $P_i \in [0, p_i^{\max})$, we conclude that $\epsilon_i \in [0,1)$ for $i = 1, 2, \ldots, n$, so that $\epsilon \in \mathcal{E}$. ∎

IV. REALIZABLE REGION

Here we show that the set of attainable protein concentrations given by $\mathcal{P}$ in (S11) lie within $\mathcal{S}$ in (S19).

Theorem 1. *Considering* $\mathcal{P}$ *and* $\mathcal{S}$ *defined in* (S11) *and* (S19)*, respectively, we obtain that* $\mathcal{P} \subseteq \mathcal{S}$.

Proof: With $\mathcal{P}_\epsilon$ defined in (S14), we have $\mathcal{P}_\epsilon = \mathcal{P}$ by Lemma 1, so that it is sufficient to show that $\mathcal{P}_\epsilon \subseteq \mathcal{S}$ to prove $\mathcal{P} \subseteq \mathcal{S}$. To this end, fix $\epsilon \in \mathcal{E}$ and let $p = A_\epsilon(\epsilon)$. If we can show that $p \in \mathcal{S}_i$ for $i = 1, 2, \ldots, n$, it implies that $p \in \mathcal{S}$ since $\mathcal{S} = \cap_{i=1}^{n} \mathcal{S}_i$ by Lemma 2, yielding $\mathcal{P}_\epsilon \subseteq \mathcal{S}$.

To show that $p \in \mathcal{S}_i$ for $i = 1, 2, \ldots, n$, define

$$\alpha_i = \frac{\kappa_i}{x + \kappa_i}, \qquad \beta_i = \frac{k_i}{y + k_i}, \qquad \epsilon_i' = \alpha_i\beta_i\epsilon_i, \tag{S22}$$

so that (S3)–(S4) become

$$x = \frac{X}{1 + W_x + \sum_{i=1}^{n} \frac{\eta_i}{\kappa_i}\epsilon_i'}, \quad y = \frac{Y}{1 + \sum_{i=1}^{n} \frac{\gamma_i\eta_i}{\delta_i} \frac{1}{\kappa_i k_i}\epsilon_i' x}.$$

As a result, with Q_i from (S16) and with $R_i' = [\gamma_i\eta_i X/(\delta_i\kappa_i k_i) + \eta_i/(\beta_i\kappa_i)]/(1 + W_x)$, we can write p_i in (S5) as

$$p_i = \frac{Q_i\epsilon_i'}{1 + \sum_{i=1}^{n} R_i'\epsilon_i'}. \tag{S23}$$

Furthermore, introduce $\tilde{p}_i = (Q_i\epsilon_i')/(1 + \sum_{i=1}^{n} R_i\epsilon_i')$ and let $\hat{p} = (\hat{p}_1, \hat{p}_2, \ldots, \hat{p}_n)^T$ where $\hat{p}_i$ is given by (S15).

The fact that $\alpha_i, \beta_i \in (0,1)$ yields $\epsilon_i' \in [0, \epsilon_i)$ by (S22) and $R_i \in (0, R_i')$ by (S16). Since $\epsilon_i' \in [0, \epsilon_i)$ implies $\tilde{p}_i < \hat{p}_i$, and similarly, $R_i \in (0, R_i')$ yields $p_i < \tilde{p}_i$, we obtain

$$0 \leq p_i < \tilde{p}_i < \hat{p}_i. \tag{S24}$$

Furthermore, from Lemma 2 we have

$$\frac{\hat{p}_i}{p_i^{\max}} + \sum_{\substack{j=1 \\ j\neq i}}^{n} \frac{\hat{p}_j}{p_j^{\infty}} - 1 < 0, \tag{S25}$$

and combining (S24)–(S25) yields

$$\frac{p_i}{p_i^{\max}} + \sum_{\substack{j=1 \\ j\neq i}}^{n} \frac{p_j}{p_j^{\infty}} < \frac{\hat{p}_i}{p_i^{\max}} + \sum_{\substack{j=1 \\ j\neq i}}^{n} \frac{\hat{p}_j}{p_j^{\infty}} < 1. \tag{S26}$$

We have $p_i \geq 0$ by (S24). Together with (S26) this implies that $p \in \mathcal{S}_i$ for $i = 1, 2, \ldots, n$ by (S18), concluding the proof. ∎

V. TYPICAL RANGE OF PARAMETERS

The dissociation constant of the T7 RNAP to its promoter is approximately 200nM [7], and since this binding is considerably stronger than that of bacterial RNAP, we conclude that $\kappa_i \gg 200$nM, suggesting $x \ll \kappa_i$ as $x \approx 100$nM.

According to [8], as many as 20 RNAP molecules can simultaneously transcribe a gene. Instead of having one gene recruiting a maximum of ω RNAP molecules, we consider ω genes allowed to recruit at most one RNAP at a time, as if the DNA copy number was $\omega\eta$ instead of η (we use a low-range value of $\omega = 5$ denoting the number of RNAP molecules simultaneously transcribing a gene). Similarly, according to [3], several ribosomes can simultaneously translate each mRNA, up to a few dozen depending on the growth rate. Instead of having m mRNA molecules, each of which can be bound to ϕ ribosomes at any given time, we consider ϕm mRNA molecules allowed to be bound to a single ribosome. This can be achieved by considering the effective production rate $\phi\gamma$ instead of γ (we use a low-range value of $\phi = 5$ denoting the number of translations per mRNA).

Considering the typical value of biochemical parameters given in Tab. S1 with $k = 1000$nM, we obtain $p \approx 10\mu$M, which is comparable to the concentration of one of the most abundant proteins in *E. coli* [9]. Therefore, we approximate the binding of ribosomes to the RBS of the mRNA to be significantly weaker than 1000nM, so that $k_i \gg 1000$nM. Combining this with the fact that the concentration of free ribosomes is $y = 1300$nM suggests that $y \ll k_i$.

TABLE S1

TYPICAL VALUES OF BIOCHEMICAL PARAMETERS

Parameter	Value	Unit	References
X	1300	nM	[2]
Y	1300	nM	[3], [4]
W_x	12	-	[2]
κ_i	1000	nM	[7]
δ_i	10	hr^{-1}	[10]
γ_i	500	hr^{-1}	[3], [11], [8]
π_i	1500	hr^{-1}	[3], [11]
λ_i	1	hr^{-1}	[12]

REFERENCES

[1] A. Gyorgy and D. Del Vecchio, Limitations and trade-offs in gene expression due to competition for shared cellular resources, *in Proc. IEEE Conf. on Decision and Control*, 2014

[2] S. Klumpp and T. Hwa, Growth-rate-dependent partitioning of RNA polymerases in bacteria, *PNAS*, vol. 105, 2008, pp. 20245-50.

[3] H. Bremer and P.P. Dennis, Modulation of chemical composition and other parameters of the cell by growth rate, *Escherichia coli and Salmonella: cellular and molecular biology*, vol. 2, 1996, pp. 1553-69.

[4] A.D. Tadmor and T. Tlusty, A coarse-grained biophysical model of *E. coli* and its application to perturbation of the rRNA operon copy number, *PLOS Computational Biology*, vo. 4, 2008.

[5] M. Scott, C.W. Gunderson, E.M. Mateescu, Z. Zhang and T. Hwa, Interdependence of cell growth and gene expression: origins and consequences, *Science*, vol. 330, no. 6007, 2010, pp. 1099-1102.

[6] J.E. Marsden, *Elementary classical analysis*. W.H. Freeman and Company, San Francisco; 1974.

[7] V.L. Tunitskaya and S.N. Kochetkov, Structural-functional analysis of bacteriophage T7 RNA polymerase, *Biochemistry (Moscow)*, vol. 67, no. 10, 2002, pp. 1124-35.

[8] H. Bremer, P.P. Dennis and M. Ehrenberg, Free RNA polymerase and modeling global transcription in *Escherichia coli*", *Biochimie*, col. 85, no. 6, 2003, pp. 597-609.

[9] T. Van den Boom and J.E. Cronan Jr., Genetics and regulation of bacterial lipid metabolism, *Annu Rev Microbiol*, vol. 43, no. 1, 1989, pp. 317-43.

[10] J.A. Bernstein, A.B. Khodursky, P.-H. Lin, S. Lin-Chao and S.N. Cohen, Global analysis of mRNA decay and abundance in *Escherichia coli* at single-gene resolution using two-color fluorescent DNA microarrays, *PNAS*, vol. 99, no. 15, 2002, pp. 9697-9702.

[11] R.Y. Tsien, The green fluorescent protein, *Annual review of biochemistry*, vol. 67, no. 1, 1998, pp. 509-44.

[12] G. Kramer, R.R. Sprenger, M.A. Nessen, W. Roseboom, D. Speijer, L. de Jong, M.J.T. de Mattos, J.W. Back and C.G. de Koster, Proteome-wide alterations in *Escherichia coli* translation rates upon anaerobiosis, *Molecular & Cellular Proteomics*, vol. 9, no. 11, 2010, pp. 2508-16.