Applications of Little’s Law to stochastic models of gene expression

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(Dated: July 13, 2010)

The intrinsic stochasticity of gene expression can lead to large variations in protein levels across a population of cells. To explain this variability, different sources of mRNA fluctuations (‘Poisson’ and ‘Telegraph’ processes) have been proposed in stochastic models of gene expression. Both Poisson and Telegraph scenario models explain experimental observations of noise in protein levels in terms of ‘bursts’ of protein expression. Correspondingly, there is considerable interest in establishing relations between burst and steady-state protein distributions for general stochastic models of gene expression. In this work, we address this issue by considering a mapping between stochastic models of gene expression and problems of interest in queueing theory. By applying a general theorem from queuing theory, Little’s law, we derive exact relations which connect burst and steady-state distribution means for models with arbitrary waiting-time distributions for arrival and degradation of mRNAs and proteins. The derived relations have implications for approaches to quantify the degree of transcriptional bursting and hence to discriminate between different sources of intrinsic noise in gene expression. To illustrate this, we consider a model for regulation of protein expression bursts by small RNAs. For a broad range of parameters, we derive analytical expressions (validated by stochastic simulations) for the mean protein levels as the levels of regulatory small RNAs are varied. The results obtained show that the degree of transcriptional bursting can, in principle, be determined from changes in mean steady-state protein levels for general stochastic models of gene expression.

INTRODUCTION

The intrinsic stochasticity of biochemical reactions involved in gene expression can give rise to large variations in protein levels across an isogenic population of cells [1, 2]. Variations in protein levels, in turn, can give rise to phenotypic heterogeneity and non-genetic individuality in a population of cells [3]. The potential benefits of such phenotypic heterogeneity have been discussed for diverse systems [4]. Correspondingly there has been considerable effort focusing on uncovering molecular mechanisms which drive gene expression ‘noise’ as a source of phenotypic heterogeneity.

High variability in protein levels has generally been attributed to fluctuations in mRNA synthesis [5-7]. To elucidate the source of mRNA fluctuations, two distinct models have been proposed [8]. In one case, mRNA synthesis is modeled as a Poisson process (Poisson scenario) and the high variability in protein levels is related to low abundance and infrequent synthesis of mRNAs [9]. In the other case, fluctuations are primarily driven by the slow kinetics of promoter switching between active and inactive states (Telegraph scenario) with mRNA synthesis occurring only during the active stage [8, 10]. Recent work has further generalized these models for gene expression to include the effects of processes that can give rise to ‘gestation’ and ‘senescence’ periods for mRNA birth and decay [11]. These terms derive from the observation that both creation and degradation of cellular macromolecules (mRNAs/proteins) often involve multiple biochemical steps. Correspondingly, the waiting-time distributions for these processes are more general than simple exponential distributions which are characteristic of single-step Poisson processes. Since the observed noise in protein levels can include contributions from different sources (e.g. transcriptional bursting as well as gestation and senescence) most single-cell measurements of steady-state protein distributions cannot be used to determine the source of fluctuations in mRNA synthesis.

Recent studies have determined the variation of noise in protein expression as a function of mean protein abundance for several genes [6, 7]. The observed scaling relationship is consistent with both the Poisson and Telegraph scenario models in the limit that protein production occurs in infrequent random bursts [6, 12]. Furthermore, advances in single-molecule techniques have led to studies monitoring real-time synthesis of proteins in single cells [13, 14]. Protein expression was indeed seen to occur in random bursts with a mean separation between bursts that is large compared to typical mRNA lifetimes [13, 14]. Given these features, it is of interest to consider whether quantification of protein burst distributions can discriminate between the two scenarios for mRNA synthesis. For the Poisson scenario, the observed burst is a consequence of translation from a single mRNA, whereas for the Telegraph scenario, it is produced from a random burst of mRNAs synthesized when the promoter is in the active state. While the underlying mRNA burst distributions can thus be distinct for the two scenarios, it can be shown that observations of protein burst distribution do not uniquely identify the underlying mRNA burst distribution [15].

Given that protein steady-state and burst distributions cannot discriminate between the Poisson and Telegraph scenarios, it has been argued that dynamic measurements of the number of mRNAs in single cells are needed.
Such methods have indeed been developed in recent years [2–16], and have been used to quantify the degree of transcriptional bursting. In this context, it would be of interest to derive equations relating burst and steady-state distribution means for both mRNAs and proteins. Such relations can provide useful checks for experimental approaches for measuring mRNA/protein burst distribution means. Furthermore they can also suggest alternative approaches which allow inference of the underlying mRNA burst distribution. This work focuses on deriving such relations between the means of mRNA/protein burst and steady-state distributions and exploring their consequences for approaches to quantify the degree of transcriptional bursting.

In this paper, we consider a mapping between general stochastic models of gene expression [11] and problems of interest in queueing theory. By applying a general theorem from queueing theory, Little’s Law, we derive exact relations connecting mRNA/protein burst and steady-state distribution means for stochastic models of gene expression with arbitrary waiting-time distributions for arrival and degradation of mRNAs and proteins. Furthermore the derived relations can be used to show how mRNA burst distributions can be inferred from measurements of mean protein levels by introducing an additional interaction in the reaction scheme. Specifically, we consider a reaction scheme that includes interaction between mRNAs and regulatory genes called small RNAs. In bacteria, small RNAs have been studied extensively in recent years [17] in part due to the critical roles they play in cellular post-transcriptional regulation in response to environmental changes. The results derived in this work, besides the potential applications for quantifying the degree of transcriptional bursting, also provide insight into small-RNA based regulation for specific parameter ranges.

MODEL AND RESULTS

Connecting burst and steady-state means

We begin by considering the minimal reaction scheme for translation from mRNAs

\[ M \xrightarrow{k_p} M + P; \quad M \xrightarrow{\mu} \emptyset; \quad P \xrightarrow{\mu_p} \emptyset; \]  

(1)

A single burst corresponds to proteins produced from the underlying mRNA burst distribution until decay of the last mRNA. For the Poisson process, mRNA transcription occurs with constant probability per unit time \( k_m \). On the other hand, for the Telegraph process, mRNA transcription occurs with constant rate \( k_m \) only when the DNA is in the active (ON) state; once it transitions from the ON state to the inactive OFF state (with rate \( \alpha \)) no mRNA transcription can occur until it transitions back from the OFF state to the ON state (with rate \( \beta \)). Note that in the limit \( \beta \ll \alpha \), mRNAs will be produced in infrequent bursts. Thus the Poisson process gives rise to only protein bursts, whereas the Telegraph process gives rise to both mRNA and protein bursts. It is interesting to note that the mRNA burst distribution for both the Poisson and Telegraph scenarios can be represented by the conditional geometric distribution; specifically by considering bursts conditional on production of at least one mRNA [15]. This can be understood as follows: the mRNA burst distribution is the number of mRNAs produced in the active state before transition to the inactive state. Let us take the initial condition to correspond to the transition from the inactive (OFF) state to the active (ON) state i.e. at \( t = 0 \) the DNA has just transitioned to the ON state. Now the next reaction that can occur either results in the production of a mRNA (with rate \( k_m \)) or a transition to the OFF state (with rate \( \alpha \)). The probability of the next reaction being protein production is \( \frac{k_m}{k_m + \alpha} \), whereas the probability that it is a transition to the OFF state is \( \frac{\alpha}{k_m + \alpha} \). If we set \( p = \frac{\alpha}{k_m + \alpha} \), the number of mRNAs produced (\( m \)) before the transition to the OFF state, conditional on the production of at least 1 mRNA, is given by

\[ \pi_m(m) = (1 - p)^{m-1}p, \quad m \geq 1, \]  

(2)

\[ \pi_m(0) = 0. \]  

(3)

For the conditional geometric distribution given above, the mean is given by

\[ m_b = \frac{1}{p}. \]  

(4)

For the Poisson scenario (\( p = 1 \)), a single mRNA is produced per burst, which corresponds to the conditional geometric distribution with mean \( m_b = 1 \). The Telegraph scenario also gives rise to a conditional geometric distribution for mRNA bursts, but with mean \( m_b > 1 \). Thus, determination of the degree of transcriptional bursting (\( m_b \)) can discriminate between the Poisson and Telegraph scenarios for intrinsic noise in gene expression.

The general model for gene expression that we analyze is as follows. Bursts of protein expression result due to translation from the underlying mRNA burst, which has a conditional geometric distribution with mean \( m_b \). The number of proteins produced from different mRNAs are taken to be independent random variables. The decay time for mRNAs and proteins is assumed to be drawn from arbitrary waiting-time distributions with means \( \tau_m \) and \( \tau_p \) respectively. Likewise, the waiting-time distribution between consecutive bursts is a random variable drawn from an arbitrary distribution with mean \( \tau_b \). Correspondingly, the average arrival rate for bursts is given by \( k_b = \frac{1}{\tau_b} \). Since the waiting-time distributions are arbitrary, effects due to gestation and senescence of mRNAs and proteins [11] are included. For this setup, we will derive analytical relations which can be used to determine...
mean mRNA lifetime ($\tau$) and thereby to quantify the degree of transcriptional bursting.

We begin with the observation that the processes considered in the above model have exact analogs in problems of interest in queueing theory. For example, the creation of proteins corresponds to the arrival of customers in queueing models [18]. On the other hand, the service-time distribution corresponds to the waiting-time for the customer to depart the system, making it the analog of the waiting-time distribution for degradation of proteins. Given that degradation of each mRNA/protein is independent of other mRNAs/proteins in the system, the mapping corresponds to queueing systems with infinite servers. This can be seen as follows. In infinite server queues, since the number of servers is unlimited, each customer is associated with a server immediately upon arrival. This effectively implies that each customer is served independently of the others, which for the gene expression model is equivalent to the assumption that mRNAs/proteins are degraded independently.

A general theorem from queueing theory, Little’s Law [18], states that the average number of customers in the system ($L$), the mean arrival rate ($\lambda$) and the mean waiting time of a customer in the system ($W$) are related by $L = \lambda W$. The remarkable feature of Little’s Law is that it holds regardless of the specific forms of the arrival and departure processes. When applied to stochastic gene expression models, this implies that the processes leading to mRNA/protein can be arbitrary, e.g. including gestation and senescence effects.

We now apply Little’s Law to derive an equation relating mRNA burst and steady-state distribution means. The arrival rate of mRNA bursts is driven by an arbitrary stochastic process with average arrival rate $k_b$. The decay process of mRNA is also assumed to be driven by an arbitrary stochastic process with average decay time $\tau_m$. Employing Little’s Law [18], we obtain a relation between the mean mRNA burst size $m_b$ and the average number of mRNAs in the steady state:

$$\langle m \rangle = \lambda \tau_m,$$  (5)

where $\lambda$ is average arrival rate of the mRNAs, which is given by

$$\lambda = m_b k_b$$  (6)

Hence, we derive that the steady-state distribution mean for mRNAs is related to the mean mRNA burst size by

$$\langle m \rangle = m_b k_b \tau_m$$  (7)

Both the mean steady-state mRNA levels ($\langle m \rangle$) and the mean mRNA lifetime ($\tau_m$) can be determined experimentally using standard procedures. Eq. 7 implies that the degree of transcriptional bursting can then be determined by estimating the mean burst arrival rate ($k_b$), which can be done using single-molecule approaches. Such a procedure was used in Ref. [14] to estimate the degree of transcriptional bursting, with the assumption of constant mRNA arrival rates and decay rates. Eq. 7 indicates that, even if this is not the case and arbitrary gestation and senescence periods are considered, the above procedure remains a valid approach to determine the degree of transcriptional bursting $m_b$. Alternatively, since the above relation is valid for arbitrary stochastic processes governing mRNA arrival and decay, it can serve as a useful consistency check for different experimental approaches for quantifying mRNA burst and steady-state distributions.

Using Little’s Law we can also relate the steady-state protein distribution mean to the burst mean following similar logic. Since the average arrival rate of proteins is given by $\langle m \rangle k_p$, we derive

$$P_s = \langle m \rangle k_b \tau_p,$$  (8)

where $k_p$ and $\tau_p^{-1}$ are average synthesis and decay rates of the proteins. The above equation can be recast in terms of the mean number of proteins produced in a single burst $P_b$ (which is related to the mRNA burst distribution mean by $P_b = m_b k_p \tau_m$). Since the mean arrival rate of proteins is given by $k_b P_b$, we have

$$P_s = k_b P_b \tau_p$$  (9)

It is noteworthy that this simple relation is valid for arbitrary gestation and senescence waiting-time distributions. It establishes that the mean steady-state protein level only depends on the average protein arrival and degradation rates and is independent of the higher moments of the corresponding waiting-time distributions. Thus, it explains the observation in Ref. [11] that gestation and senescence do not affect the average susceptibility to changes in parameters.

Another important consequence of Eq. 9 is that processes that alter the burst distribution mean without affecting protein degradation times or burst arrival times will produce a proportionate change in the steady-state distribution mean. Thus, regulatory interactions which are sensitive to the degree of transcriptional bursting and alter protein burst distributions will produce proportionate changes in protein steady-state distribution means. This, in turn, suggests the possibility of obtaining signatures of transcriptional bursting by observing changes in steady-state protein distribution means upon regulation. To explore this possibility, let us consider how regulation by small RNAs modulates protein burst distributions.

### Regulation by small RNAs

We consider regulation by small RNAs (sRNAs) based on a coarse-grained model (Fig. 1) studied previously
which applies to sRNAs that regulate mRNA targets stoichiometrically due to coupled degradation \[22\].

Synthesis of sRNAs is taken to be a Poisson process with constant rate \(k_s\) and the sRNA degradation rate is also taken as constant (\(\mu_s\)) in the following analysis. The parameter \(\gamma\) controls mutual degradation of mRNAs interacting with sRNAs. As in the previous section, mRNAs are created in bursts, with the average rate of arrival for bursts given by \(k_s\). If \(k_s\mu_s \ll 1\), i.e. if the sRNA lifetime is small compared to the mean arrival time between bursts, the distribution of sRNAs prior to a mRNA burst can be approximated by the steady-state distribution of sRNAs in the absence of mRNAs. Given this approximation, we wish to derive expressions for the protein burst distribution in the presence of sRNAs. This is, in general, analytically intractable. However by employing further approximations which are valid for a range of parameters we can obtain analytical expressions for the burst distribution. Specifically, we assume that synthesis of new sRNAs during a burst can be ignored, i.e. no new sRNAs are created in the time interval between mRNA creation and decay. Furthermore, we consider \(\gamma \tau_m \gg 1\) such that mRNA degradation in the presence of sRNAs is assumed to occur due to mutual degradation with a sRNA rather than natural decay with average rate \(\mu_m = \frac{1}{\tau_m}\). Given that these approximations are valid, a simple analytic expression for the mean regulated protein levels can be obtained as a function of mean sRNA levels as shown below.

As indicated in the reaction scheme in Fig. 1, a pair of molecules of mRNA and sRNA can combine and be degraded rapidly with rate \(\gamma\). We first consider the limit \(\gamma \to \infty\). In this case, regulation by sRNAs results in an instantaneous modification of the distribution of mRNAs just after the burst. The mRNA burst distribution prior to interaction with sRNAs is given by \(\pi_m(m)\) (Eq. 2). The modified mRNA burst distribution after interaction with sRNAs (\(\tilde{\pi}_m(m)\)) is given by

\[
\tilde{\pi}_m(m) = \sum_{n=0}^{\infty} \rho(n)\pi_m(m+n), \quad m \geq 1,
\]

where \(\rho(n)\) is the probability of finding \(n\) sRNA molecules at the time of burst. Any burst of \(m\) mRNA molecules instantly becomes an effective burst of \(m-n\) mRNA molecules (for \(m > n\)) due to coupled degradation with \(n\) sRNAs. If \(m \leq n\), the mRNA burst after the regulation will be effectively an ‘empty’ burst. The probability of an empty burst is given by

\[
\tilde{\pi}_m(0) = 1 - \sum_{m=1}^{\infty} \tilde{\pi}_m(m).
\]

Since the unregulated mRNA burst distribution is geometric (with parameter \(p\), say), we derive

\[
\tilde{\pi}_m(m) = \pi_m(m) \sum_{n=0}^{\infty} (1-p)^n \rho(n) = G(1-p)\pi_m(m), \quad m \geq 1,
\]

where \(G(1-p)\) is the generating function of sRNA probability distribution \(\rho(n)\), evaluated at the point \(1-p\). Using Eq. 11 we derive

\[
\tilde{\pi}_m(0) = 1 - G(1-p),
\]

The regulated mRNA burst distribution is thus a conditional geometric distribution as in the unregulated case, but with modified average arrival rate \(\tilde{k}_m = G(1-p)k_m\). This is because \(1 - \tilde{\pi}_m(0) = G(1-p)\) is the probability that the regulated burst results in at least 1 mRNA. Therefore, the average number of mRNAs in the steady state for the regulated case is given by (according to the equation Eq. 7)

\[
\langle n \rangle = m_b \tilde{k}_m \tau_m = G(1-p)(1/m).
\]

We denote by \(P_b(n_s)\) the mean burst size for proteins in the presence of sRNAs, where \(n_s = k_s/\mu_s\). Using the equations Eq. 8\(\tilde{\pi}_m(m)\) for mRNA’s steady state average, we derive in the limit of fast coupled degradation (\(\gamma \to \infty\))

\[
P_s(n_s) = G(1-p)P_s(0).
\]

Taking the sRNA distribution prior to the burst (\(\rho(n)\)) to be a Poisson distribution with mean \(n_s = k_s/\mu_s\), and given that the mean mRNA burst size is given by \(m_b = 1/p\) (Eq. 4), we derive

\[
\frac{P_b(n_s)}{P_b(0)} = e^{-n_s/m_b}
\]

Thus, if the burst mean \((P_b)\) is determined along with \(n_s\), the above relation determines \(m_b\) and hence the degree of transcriptional bursting. Eq. 9 further implies that

FIG. 1. The kinetic scheme for regulation of protein production by small RNAs with coupled degradation rate \(\gamma\).
the ratio of protein steady-state means for regulated to unregulated cases \( \frac{m_b}{m_u} \) is equal to the corresponding ratio for the burst means in Eq. 16. This in turn implies that the mean transcriptional burst size \( m_b \) can be determined by considering changes in mean steady-state protein levels. Taken together, these results provide a novel procedure for determining \( m_b \).

The proposed procedure has been computationally validated for a range of parameters using stochastic simulations (Fig. 2). Specifically, we set up simulations based on the standard Gillespie algorithm \[23\] wherein the next reaction is drawn from an exponential distribution. To consider effects such as mRNA senescence, we model mRNA degradation as a multi-step process, wherein the waiting-time distribution for each step is drawn from an exponential distribution such that the degradation time for mRNAs follows a Gamma distribution (see Appendix). Similarly, mRNA arrival was simulated as a multi-step process with gamma waiting-time distribution between mRNA arrival bursts. The output from the simulations is the mean steady-state protein levels as a function of the mean mRNA levels \( n_s \), where the mean sRNA levels are varied by increasing the sRNA creation rate \( k_s \). Provided that the system parameters are consistent with the following constraints: \( \gamma \gg \mu_m \gg \mu_s \), simulations indicate that the transcriptional burst size \( m_b \) can be predicted with reasonable accuracy from the ratio of measured protein steady-state means for regulated to unregulated cases as discussed above. The errors in the estimate for \( m_b \) using the above procedure are related to the validity of the approximations made and are discussed further in the Appendix. Provided that regulatory small RNAs can be designed with parameters subject to the constraints noted, the relative error in estimating \( m_b \) is small and thus we can determine the degree of transcriptional bursting and clearly distinguish between the Poisson and Telegraph scenarios. The parameter ranges for validity of the above analysis are accessible experimentally based on previous work, e.g. high values of \( \gamma \) relative to the natural degradation rate \( \mu_m \) are expected for the sRNA RhyB \[24\], and mRNA burst arrival rates which are small compared to the mRNA degradation rate have also been reported \[14\]. Finally, we note that it would be of interest to apply the preceding analysis to systems which show high degree of transcriptional bursting primarily arising from random activation and inactivation of the promoter state \[25\]. In particular, it was observed \[24\] that increasing concentrations of a transcriptional activator resulted in increasing the mean burst size rather than affecting the burst frequency. Since the procedure proposed in this work is an independent approach to determine the burst mean, it would be of interest to further analyze the above system using the analysis proposed in the current work.

**SUMMARY AND CONCLUSIONS**

In summary, we have considered a generalized model of gene expression with bursty production of mRNAs and proteins. Since very different stochastic processes can lead to steady-state distributions that are experimentally indistinguishable, the degree of transcriptional bursting cannot be inferred from steady-state protein distributions. In light of this, it has been argued that determination of transcriptional bursting requires dynamic measurements of mRNA molecules in single cells \[11, 12, 26\]. In this work, we have derived exact relations connecting mRNA/protein burst and steady-state distribution means which are valid for arbitrary gestation and senescence waiting-time distributions. We further analyzed how protein burst distributions are modified due to regulation by small RNAs for a range of parameters. Our analysis computationally demonstrates an alternative procedure for quantifying transcriptional bursting, which involves measurements of changes in mean protein steady-state levels induced by interactions with small RNAs. The strategy presented can also be applied to a broader classes of biological networks whose analysis requires inference of internal variables from observations at higher levels. An alternative strategy to direct measurements of internal variables is to discriminate different possibilities for the internal variables by coupling to a controlled external interaction.

**APPENDIX**

**Finite \( \gamma \) corrections**

The analysis in the main text considered the limit \( (\gamma \to \infty) \) and we now consider corrections due to finite
γ values. Lets take a more detailed look at the protein production process during the burst. We denote the duration from the beginning of the burst to the time when sRNA or mRNA number first reaches zero as the first stage of the burst. If the mRNAs outnumber the sRNAs, excess mRNAs will be left after the coupled degradation and evolve accordingly. We call the duration from this point to the time when all mRNAs are degraded as stage two of the burst. In the case that γ → ∞, the duration of stage one will be zero and all proteins are produced in stage two of the burst. However, for finite γ value, one has to take into account proteins that have been synthesized during stage one of the burst.

In order to estimate the amount of the proteins produced on average from mRNAs that are degraded by sRNAs (stage one), we observe first that the minimal degradation rate of a single mRNA in this process is γ. This is because at least one sRNA should be present to ensure coupled degradation. Second, the total amount of mRNAs in the originating burst is greater than or equal to number of mRNAs degraded by sRNAs (since some mRNAs may decay naturally).

Hence, we can employ formula Eq. 7 in order to estimate contribution of the mRNAs decaying in coupled degradation process to overall steady state level. The upper bound of this contribution is given by

\[ \langle \delta m \rangle \sim n_m \frac{k_m}{\gamma}. \]  

(17)

Here we replaced the rate τ_m^-1 in the Eq. 7 by the minimal rate γ in order to estimate the upper limit.

Now we can use the expression Eq. 5 to get the upper bound of the proteins produced on average from the mRNAs during the coupled degradation process

\[ \delta P_s(n_s) \sim \delta m k_p \tau_p \sim \left(n_m \frac{k_m}{\gamma}\right) k_p \tau_p. \]  

(18)

Hence, the overall ratio of regulated to unregulated mean steady state levels of proteins is bounded as

\[ \delta R \sim \frac{\delta P_s(n_s)}{P_s(0)} = \frac{1}{\tau_m \gamma}, \]  

(19)

which is independent of protein’s synthesis rate k_p. Therefore, if coupled degradation process is much faster than natural mRNA decay, τ_mγ ≫ 1, we obtain δR → 0 which is validated by simulations. As we can see in Fig 3, when τ_mγ > 10 the proteins produced during stage one of the burst can be neglected and the result is almost the same as when γ → ∞. Finally we note that recent studies [24] have shown that a well-studied bacterial small RNA (RhyB) does induce rapid degradation of target mRNAs consistent with the condition τ_mγ ≫ 1.

Waiting-time distribution for multi-step processes

Previous work [11] on gestation and senescence effects in mRNA/protein production and decay considered extensions of the single-step Poisson process to multi-step processes. For the simplest case, the corresponding waiting time distribution is a Gamma distribution as derived below. Consider a multi-step process, consisting of n steps such that each step is completed with rate k. Let T denote the random variable corresponding to the waiting-time for the process to finish and let T_i be the random variable corresponding to the waiting-time for the i^{th} step. Thus we have T = \sum_i T_i, i.e. T is the sum of n identical independent random variables. Correspondingly we have F(s) = \left(\frac{e^{-ks}}{k \cdot s}ight)^n, and inverting the Laplace transform we obtain that the waiting-time distribution for the multi-step process is given by the Gamma distribution: k(kt)^{n-1} e^{-kt} \gamma (k-1).

**FIG. 3.** The relative error η of the estimated m_b derived from changes in mean protein burst levels. For different n_s and m_b values, the error is negligible when γ ≥ 10μ_m.
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