Spectral theory of stochastic gene expression: a Hilbert space framework

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Abstract

A perusal of the literature shows large discrepancies between purported exact results for the spectra of stochastic gene expression models. For self-repressing gene circuits, previous studies ([Phys. Rev. Lett. 99, 108103 (2007)], [Phys. Rev. E 83,062902 (2011)], [J. Chem. Phys. 160, 074105 (2024)], and [bioRxiv 2025.02.05.635946 (2025)]) have provided different exact solutions for the eigenvalues of the generator matrix. In this work, we propose a unified Hilbert space framework for the spectral theory of stochastic gene expression. Based on this framework, we analytically derive the spectra for models of constitutive, bursty, and autoregulated gene expression. Our results demonstrate that for infinite-dimensional operators such as in stochastic gene expression models, many conclusions in linear algebra do not apply, and one must rely on the modern theory of functional analysis.

Introduction

Over the past few decades, significant progress has been made to derive a spectral theory of stochastic gene expression. Since the mRNA and protein numbers can take any integer values, the state space of a stochastic gene expression model is usually infinite and the corresponding generator matrix of the Markovian dynamics is usually an infinite-dimensional operator [1, 2]. The spectral theory is crucial for the following two reasons. First, it is well known that the absolute value of the first nonzero eigenvalue of the generator matrix characterizes the relaxation rate of the system to the steady state [3]. Second, the spectral decomposition method has been widely used to obtain the exact time-dependent solution for stochastic gene expression models [4–6].

Within the continuous-time Markovian framework, some studies model the protein dynamics explicitly and model the gene dynamics implicitly [7, 8]. For such models, the spectral theory has been well developed for both unregulated and autoregulated genes when protein synthesis is constitutive [3], i.e. the molecules are produced one at a time. For unregulated genes, the eigenvalues are discrete and are given by

$$\lambda_n = -nd, \quad n = 0, 1, 2 \cdots ,$$

where d is the rate of protein degradation. By analyzing the properties of the first nonzero eigenvalue, it has been shown that positive autoregulation always slows down the relaxation kinetics to the steady state, while negative autoregulation always speeds it up [3]. In addition, the time-dependent solution for an autoregulatory feedback loop has been obtained when all eigenvalues of the Markovian model are known [9].

Other studies have considered more realistic models where both the gene and protein dynamics are modelled explicitly [10–15]. For such models, the spectral theory has also been examined for both unregulated and autoregulated

genes [5, 6, 16–18]. Since now the gene switching dynamics is taken into account, for unregulated genes, there are two sets of eigenvalues [6]:

$$\lambda_{1,n} = -nd, \quad \lambda_{2,n} = -(a+b+nd), \quad n = 0, 1, 2 \cdots ,$$

where d is the rate of protein degradation, and a and b are the switching rates between the active and inactive gene states. However, for autoregulatory gene circuits, results on the spectral theory do not agree with each other — previous studies have obtained different purported exact solutions of the eigenvalues. Ramos and coworkers [5, 16–18] claimed that the eigenvalues for self-repressing genes are all real numbers. However, our previous study [6] showed that the eigenvalues for the same system are the roots of a non-trivial continued fraction equation and are not always real as previously claimed. Thus far, there is a lack of a unified mathematical framework for the spectral theory of stochastic gene expression models that can be used to clarify which eigenvalues are correct and which are incorrect.

In this work, we propose a rigorous Hilbert space framework for the spectral theory of stochastic gene expression models. Based on this framework, we analytically derive the spectra for three classical models, including models of constitutive genes, bursty genes, and self-repressing genes. For self-repressing genes, our results show that the eigenvalues given in [6] are correct and can be complex numbers, while the real eigenvalues given in [5, 16–18] are incorrect. In particular, we demonstrate that for infinite-dimensional operators such as in stochastic gene expression models, many conclusions in linear algebra do not apply, and one must rely on the modern theory of functional analysis.

Results

Consider the stochastic model of a self-repressing gene, where the protein expressed from a gene represses its own transcription (Fig. 1(a)). Let G and G^* denote the inactive and active states of the gene, respectively, and let P denote the corresponding protein. The reaction scheme for the self-repressing gene is as follows:

$$\begin{aligned} G \xrightarrow{a} G^*, \quad G^* + P \xrightarrow{\nu} G + P, \\ G^* \xrightarrow{s} G^* + P, \quad P \xrightarrow{d} \varnothing. \end{aligned} \tag{1}$$

Here a is the switching rate from the inactive to the active gene state, ν is the binding rate of protein to the gene in its active state which characterizes the strength of negative feedback, s is the synthesis rate of protein when the gene is active, and d is the degradation rate of protein. We emphasize that this model is a simplified version of reality so that the calculations are analytical tractable and simple. Here we assume that there is no change in the protein number during gene activation and inactivation. However, in reality, the protein number decreases by one when a protein copy binds to a gene and increases by one when unbinding occurs [11]. In other words, the present model ignores the protein-gene binding fluctuations and hence it may not be accurate when the protein number is very small or when the feedback strength is very strong [15, 19].

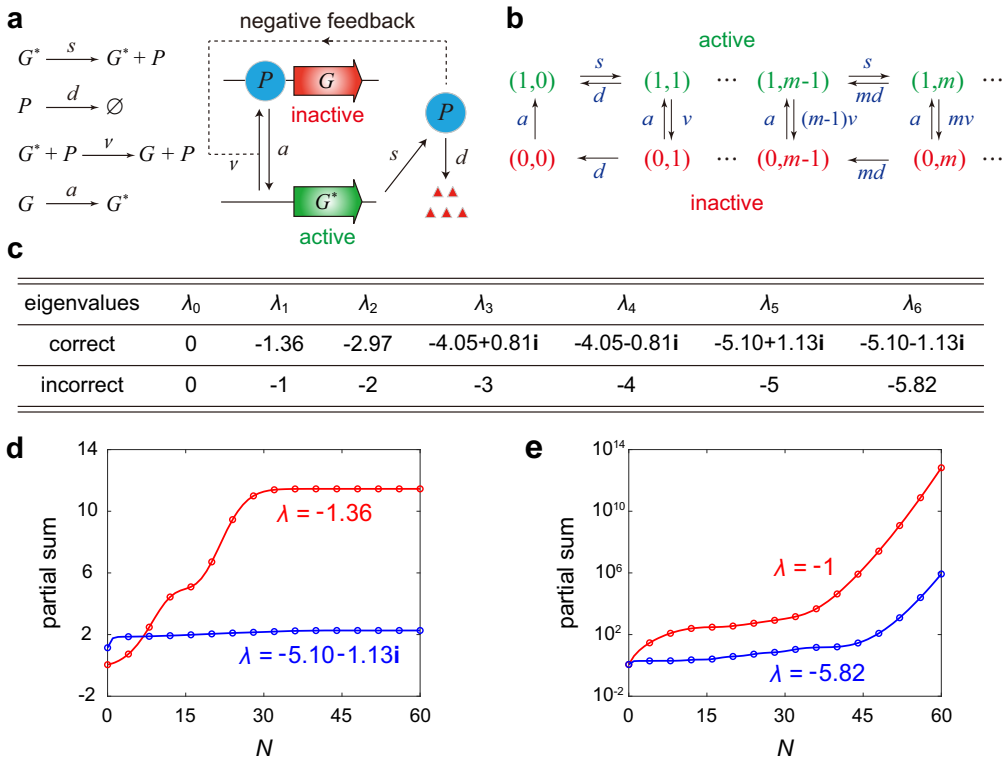
The microstate of the gene of interest can be represented by the ordered pair (i, m), where i is the state of the gene with $i = 0, 1$ corresponding to the inactive and active states, respectively, and m is the number of protein. The stochastic gene expression dynamics is described by the Markov jump process illustrated in Fig. 1(b) with an infinite-dimensional generator matrix. In the Letter [16], the authors computed the spectra for a self-repressing gene. The authors claimed that the generator matrix Q of the Markovian dynamics had a set of eigenvalues (see Eq. (26) in [16]):

$$\lambda_{1,n} = -n(d+\nu) - a - \frac{s\nu}{d+\nu}, \quad n = 0, 1, 2, \cdots , \tag{2}$$

In their subsequent work [5, 17], they gave another set of eigenvalues for the same model (see Eq. (9) in [5] and Eq. (5) in [17]):

$$\lambda_{2,n} = -nd, \quad n = 0, 1, 2, \cdots , \tag{3}$$

In particular, the two sets of eigenvalues are all real numbers. A "proof" of this result was provided in a recent paper using a linear algebraic method [18]. The logic of the linear algebraic method is as follows: if one can find a square matrix Φ and a diagonal matrix Λ such that $\Phi Q = \Lambda \Phi$, then the diagonal elements of Λ are all eigenvalues of the generator matrix Q. We emphasize that the linear algebraic method is indeed valid if Q is a finite-dimensional matrix; however, it may not work if Q is an infinite-dimensional matrix. In the Appendix, we have proved that for any diagonal matrix Λ (its diagonal elements do not need to be all eigenvalues), if Q is infinite-dimensional then one can always find a matrix Φ such that $\Phi Q = \Lambda \Phi$.



eigenvalues	λ_0	λ_1	λ_2	λ_3	λ_4	λ_5	λ_6
correct	0	-1.36	-2.97	-4.05+0.81**i**	-4.05-0.81**i**	-5.10+1.13**i**	-5.10-1.13**i**
incorrect	0	-1	-2	-3	-4	-5	-5.82

Figure 1: **Spectra for a self-repressing gene**. **(a)** Model of a self-repressing gene. Here G and G^* denote the inactive and active states of the gene, respectively, and P denotes the protein. Note that this is a simplified model for self-repression that is convenient for calculation purposes. **(b)** Transition diagram for the Markovian dynamics of the model. **(c)** Comparison of the correct and incorrect eigenvalues of the generator matrix of the model. The spectra given in Eq. (6) are correct, while those given in Eqs. (2)-(3) are incorrect. The model parameters are chosen as $s = 20$, $d = 1$, $a = 4$, $\nu = 0.1$. **(d)** Partial sum $\sum_{i=0}^{1}\sum_{m=0}^{N} |\psi_{i,m}|^2/\pi_{i,m}$ as a function of N for $\lambda = -1.36$ and $\lambda = -5.10 - 1.13\mathbf{i}$. **(e)** Same as (d) but for $\lambda = -1$ and $\lambda = -5.82$. In (d),(e), the values of λ are chosen to be the first and sixth nonzero correct and incorrect eigenvalues shown in (c), respectively. It is clear that the power series converges for the correct eigenvalues and diverges for the incorrect eigenvalues.

Here we will show that $\lambda_{1,n}$ and $\lambda_{2,n}$ as given by Eqs. (2)-(3) are not the true eigenvalues of Q. To see this, we propose a Hilbert space framework for the spectral theory of stochastic gene expression models. In modern functional analysis, the eigenvalues and eigenvectors of an infinite-dimensional operator must be defined within a given Hilbert or Banach space. A common choice is the Hilbert space [20]:

$$l^2(\pi) = \left\{ \psi = (\psi_{i,m}) : \sum_{i=0}^{1} \sum_{m=0}^{\infty} |\psi_{i,m}|^2/\pi_{i,m} < \infty \right\},$$

where $\pi = (\pi_{i,m})$ is the steady-state distribution of the self-repressing gene expression model which has been obtained

exactly in [10] and is given by

$$\begin{aligned}\pi_{1,m} &= \frac{d}{s}\frac{(\alpha)_{m+1}}{(\beta)_{m+1}}\frac{w^{m+1}}{m!}\frac{{}_1F_1(\alpha+m+1;\beta+m+1;-wz_0)}{{}_1F_1(\alpha;\beta;w(1-z_0))},\\ \pi_{0,m} &= \frac{(\alpha)_m}{(\beta)_m}\frac{w^m}{m!}\frac{{}_1F_1(\alpha+m;\beta+m;-wz_0)}{{}_1F_1(\alpha;\beta;w(1-z_0))}-\pi_{1,m},\end{aligned} \tag{4}$$

where ${}_1F_1(\alpha;\beta;z)$ is Kummer's confluent hypergeometric function and

$$\alpha=\frac{a}{d},\quad \beta=\frac{a}{\nu+d}+\frac{s\nu}{(\nu+d)^2},\quad w=\frac{s}{\nu+d},\quad z_0=\frac{d}{\nu+d}. \tag{5}$$

Specifically, if there exists a row vector $\psi=(\psi_{i,m})\in l^2(\pi)$ such that $\psi Q=\lambda\psi$, then λ is as an eigenvalue of the generator matrix Q and ψ is the associated (left) eigenvector. For convenience, here we have defined left eigenvectors. Similarly, one can also consider the right eigenvectors; in this case, the Hilbert space should be chosen as the dual space of $l^2(\pi)$ [21]. The above framework is analogous to that in quantum mechanics, where any physically meaningful observable must be an Hermitian operator on a Hilbert space and its eigenvalues correspond to all possible outcomes of a measurement of the given observable.

Here we claim that all nonzero eigenvalues λ of the generator matrix Q for a self-repressing gene are the roots of the following nontrivial continued fraction equation:

$$q=\frac{R_0P_1}{(Q_1+q)-}\frac{R_1P_2}{(Q_2+q)-}\frac{R_2P_3}{(Q_3+q)-}\cdots, \tag{6}$$

where $P_n=\theta+(n-1)\epsilon$, $Q_n=n[-(n-1+\gamma)-\delta+\epsilon]$, and $R_n=-(n+1)(n+\gamma)$ with

$$\begin{aligned}q &= -\frac{(\lambda+d)(a+\lambda)}{d(\nu+d)}-\frac{[\nu(a+\lambda)+d\nu]s}{d(\nu+d)^2},\\ \theta &= -\frac{(a+d+\lambda)\nu s}{d(\nu+d)^2},\quad \gamma=\frac{a+\lambda}{\nu+d}+\frac{s\nu}{(\nu+d)^2},\\ \delta &= 2+\frac{\lambda}{d},\quad \epsilon=-\frac{\nu ds}{d(\nu+d)^2}.\end{aligned}$$

An informal derivation can be found in [6]. In the Appendix, we give a rigorous proof of this fact using the Hilbert space framework. Fig. 1(c) compares the incorrect eigenvalues given in Eqs. (2)-(3) and the correct ones given in Eq. (6). It can be seen that the eigenvalues are not always real as previously claimed in [5, 16–18]. This agrees with a well-known result that a negative feedback loop can produce oscillatory behaviors which correspond to complex eigenvalues [22, 23].

It has been previously argued [18] that the generator matrix of a self-repressing gene is self-adjoint and hence must have real eigenvalues. A well-established result in probability theory states that the generator of a Markov jump process is self-adjoint only when the system satisfies detailed balance [24, 25], i.e. the product of transition rates along any cycle is exactly equal to that along its reversed cycle, which is known as the Kolmogorov cyclic condition [26, 27]. It is easy to verify that the Markovian model shown in Fig. 1(b) does not satisfy detailed balance. Hence, its generator cannot be self-adjoint, which implies that the eigenvalues are not restricted to be real.

To further validate our result, we compute the eigenvector corresponding to each eigenvalue numerically and then check whether the corresponding eigenvector is in the Hilbert space $l^2(\pi)$. Fig. 1(d),(e) illustrate the partial sum of the power series $\sum_{i=0}^{1}\sum_{m=0}^{\infty}|\psi_{i,m}|^2/\pi_{i,m}$ with the eigenvalues being chosen as either in Eqs. (2)-(3) or as in Eq. (6). It is clear that the power series converges for the eigenvalues given in Eq. (6) (Fig. 1(d)), while the power series diverges for the eigenvalues given in Eqs. (2)-(3) (Fig. 1(e)). Our analysis highlights that for infinite-dimensional operators, many conclusions in linear algebra do not apply and we must instead rely on the theory of functional analysis.

Finally, we apply the Hilbert space framework to find eigenvalues for another two classical models: a constitutive gene expression model

$$G \xrightarrow{s} G + M, \quad M \xrightarrow{d} \varnothing,$$

and a bursty gene expression model

$$G \xrightarrow{\rho p^k (1-p)} G + kP, \quad k \geq 1, \quad P \xrightarrow{d} \varnothing.$$

Here G denotes the gene, M denotes the corresponding mRNA, and P denotes the corresponding protein. For the former model, s is the rate of mRNA synthesis and d is the rate of mRNA degradation. For the latter model, the synthesis of protein occurs in bursts with frequency ρ and random size k sampled from a geometric distribution with parameter $p \in (0, 1)$, and d is the rate of protein degradation. In the Appendix, we have applied the Hilbert space framework and rigorously proved that for both models, the eigenvalues are given by

$$\lambda_n = -nd, \quad n = 0, 1, 2 \cdots .$$

This once again demonstrates the power of the Hilbert space framework in studying the spectral structure of gene expression models.

Conclusion

In this work, we proposed a rigorous and general mathematical framework to investigate the spectral structure of models of stochastic gene expression. Our results show that for these models, the conventional linear algebraic method may not apply because of their infinite-dimensional operators. Instead for a rigorous and correct treatment we must rely on the modern theory of functional analysis — the eigenvalues and eigenvectors of the generator matrix for the Markovian model must be defined within a unified Hilbert space framework. In particular, we clarified that for autoregulatory gene circuits, the exact eigenvalues given in [6] are correct and can be complex numbers, while the real eigenvalues given in [5, 16–18] are incorrect.

Acknowledgements

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Appendix A A simple model of constitutive mRNA production

Let G denote the gene of interest and let M denote the corresponding mRNA. We first focus on a simple gene expression model with constitutive mRNA synthesis (mRNA molecules are produced one at a time) and mRNA degradation. The expression dynamics for a constitutive gene is described by the reactions (Fig. 2(a))

$$G \xrightarrow{s} G + M, \quad M \xrightarrow{d} \varnothing,$$

where s is the rate of mRNA synthesis and d is the rate of mRNA degradation. The microstate of the gene is described by the mRNA number $m = 0, 1, 2, \cdots$. The stochastic evolution of the mRNA number in a single cell is characterized

by the birth and death process shown in Fig. 2(b). Recall that it is a Markov jump process with generator matrix

$$Q = (q_{nm})_{n,m\geq 0} = \begin{pmatrix} -s & s & & & \\ d & -(d+s) & s & & \\ & 2d & -(2d+s) & \ddots & \\ & & \ddots & \ddots & \end{pmatrix},$$

where q_{mn} denotes the transition rate from microstate m to microstate n. A well-known result is that for this model, the eigenvalues of the generator matrix Q are given by [3, 18]

$$\lambda_n = -nd, \quad n = 0, 1, 2, \cdots.$$

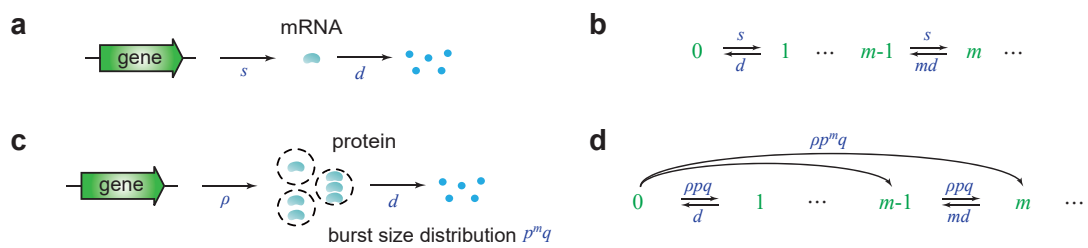

Figure 2: **Models**. **(a)** Model with constitutive mRNA synthesis and mRNA degradation. **(b)** Transition diagram of the Markovian dynamics for the model shown in (a). **(c)** Model with bursty protein synthesis and protein degradation. **(d)** Transition diagram of the Markovian dynamics for the model shown in (c).

In a recent paper [18], the author used a linear algebraic method to compute the eigenvalues for stochastic gene expression dynamics. The logic of the linear algebraic method is as follows: let Q be the generator matrix of a stochastic gene expression model; if one can find a matrix Φ and a diagonal matrix Λ such that $\Phi Q = \Lambda\Phi$, then the diagonal elements of Λ are all eigenvalues of the generator matrix Q.

We now show that the linear algebraic method proposed in [18] is questionable. To see this, we will prove that for any diagonal matrix $\Lambda = \mathrm{diag}(\lambda_0, \lambda_1, \cdots)$ (its diagonal elements do not need to be all eigenvalues), one can always find a matrix $\Phi = (\Phi_{nm})_{n,m\geq 0}$ such that

$$\Lambda\Phi = \Phi Q. \tag{7}$$

Note that Eq. (7) can be written in component form as

$$\lambda_n \phi_{nm} = \sum_{l=0}^{\infty} \phi_{nl} q_{lm} = \phi_{n,m-1} s - \phi_{nm}(md+s) + \phi_{n,m+1}(m+1)d, \tag{8}$$

where $\phi_{n,-1} = 0$ by default. To proceed, we introduce the generating functions

$$f_n(z) = \sum_{m=0}^{\infty} \phi_{nm} z^m, \quad n = 0, 1, 2, \cdots.$$

Thus, Eq. (8) can be expressed as the following differential equation:

$$\lambda_n f_n(z) = s(z-1) f_n(z) - d(z-1) f_n'(z). \tag{9}$$

For convenience, we set $\phi_{n0} = 1$, which ensures that $f_n(z) = 1$. It then follows that Eq. (9) can be solved explicitly as

$$f_n(z) = e^{sz/d}(1-z)^{-\lambda_n/d}. \tag{10}$$

Hence the components of the matrix Φ can be computed in closed form as

$$\phi_{nm} = \frac{1}{m!} f_n^{(m)}(0) = \frac{1}{m!} \sum_{l=0}^{m} C_{m,l} (\lambda_n/d)_l (s/d)^{m-l},$$

where $(x)_l = x(x+1)\cdots(x+l-1)$ denotes the Pochhammer symbol and $C_{m,l} = m!/l!(m-l)!$ denotes the combinatorial number. This implies that, regardless of how the diagonal matrix Λ is chosen, one can always find a matrix Φ such that Eq. (7) holds. Hence, even if Eq. (7) holds, we cannot conclude that the diagonal components of Λ are all eigenvalues of the generator matrix Q.

We next compute all eigenvalues for constitutive genes based on the Hilbert space framework. Consider the Hilbert space [3, 28]

$$l^2(\pi) = \left\{ \psi = (\psi_m) : \sum_{m=0}^{\infty} |\psi_m|^2/\pi_m < \infty \right\},$$

where $\pi = (\pi_m)$ is the steady-state distribution of the Markovian model. In steady state, it is well known that the mRNA number for the constitutive gene expression model shown in Fig. 2(a) has the Poisson distribution

$$\pi_m = \frac{(s/d)^m}{m!} e^{-s/d}. \tag{11}$$

Let $\psi = (\psi_m) \in l^2(\pi)$ be the eigenvector corresponding to the eigenvalue λ. For convenience, we introduce the following generating function associated with the vector $\psi = (\psi_m)$:

$$f(z) = \sum_{m=0}^{\infty} \psi_m z^m. \tag{12}$$

Similarly to Eq. (10), the generating function f can be computed exactly as

$$f(z) = e^{sz/d}(1-z)^{-\lambda/d}. \tag{13}$$

The eigenvector can then be computed by taking the derivatives of the generating function f, i.e.

$$\psi_m = \frac{1}{m!} \sum_{l=0}^{m} C_{m,l} (\lambda/d)_l (s/d)^{m-l}.$$

To find all eigenvalues of the generator matrix Q, we first focus on the case when $\lambda = -nd$ for some $n \geq 0$. In this case, the generating function $f(z) = e^{sz/d}(1-z)^n$ is holomorphic over the whole complex plane and thus the convergence radius of the power series given in Eq. (12) is ∞, which implies that (recall that the convergence radius of the power series $\sum_{m=0}^{\infty} \psi_m z^m$ is $1/\overline{\lim}_{m\to\infty} \sqrt[m]{|\psi_m|}$ [29])

$$\overline{\lim_{m\to\infty}} \sqrt[m]{|\psi_m|} = 0.$$

Hence we have $|\psi_m| \leq (1/2)^m$ when $m \gg 1$. On the other hand, when $\lambda = -nd$, the term $(\lambda/d)_l = (-n)_l$ will vanish when $l \geq n+1$. This suggests that for any $m \geq n$,

$$\begin{aligned} |\psi_m/\pi_m| &= \left| e^{s/d} \sum_{l=0}^{n} C_{m,l} (-n)_l (s/d)^{-l} \right| = e^{s/d} \left| \sum_{l=0}^{n} \frac{m!}{(m-l)!} (-1)^l C_{n,l} (d/s)^l \right| \\ &\leq e^{s/d} \sum_{l=0}^{n} C_{n,l} m^l (d/s)^l = e^{s/d} (md/s+1)^n. \end{aligned}$$

This further gives rise to

$$\sum_{m=0}^{\infty} |\psi_m|^2/\pi_m \leq e^{s/d} \sum_{m=0}^{\infty} |\psi_m|(md/s+1)^n < \infty,$$

where we have used the fact that $|\psi_m| \leq (1/2)^m$ when $m \gg 1$. This clearly shows that $\psi \in l^2(\pi)$ and thus $\lambda = -nd$ is an eigenvalue of the generator matrix Q.

We next focus on the case when $\lambda \neq -nd$ for all $n \geq 0$. In this case, $z = 1$ is a singular point of the generating function $f(z) = e^{sz/d}(1-z)^{-\lambda/d}$ and thus the convergence radius of the power series given in Eq. (12) is 1, which implies that

$$\overline{\lim_{m\to\infty}} \sqrt[m]{|\psi_m|} = 1.$$

Hence we have $\overline{\lim}_{m\to\infty} |\psi_m| 2^m \geq 1$. It then follows from Eq. (11) that

$$\overline{\lim_{m\to\infty}} |\psi_m|^2/\pi_m \geq e^{s/d} \overline{\lim_{m\to\infty}} \frac{m!}{4^m (s/d)^m} = \infty,$$

where we have used the fact that $\lim_{m\to\infty} m!/C^m = \infty$ for any $C > 0$. This shows that $\psi \notin l^2(\pi)$ and thus $\lambda \neq -nd$ is not an eigenvalue of the generator matrix Q.

In summary, we have shown that for constitutive genes, all the eigenvalues of Q are given by $\lambda_n = -nd$, $n \geq 0$. To validate this result, we illustrate the partial sum of the power series $\sum_{m=0}^{\infty} |\psi_m|^2/\pi_m$ for $\lambda = -nd$ and for $\lambda \neq -nd$ in Fig. 3. It is clear that for the former case, the power series converges (Fig. 3(a)) and hence $\lambda = -nd$ is a true eigenvalue; for the latter case, the power series diverges (Fig. 3(b)) and hence $\lambda \neq -nd$ is not an eigenvalue.

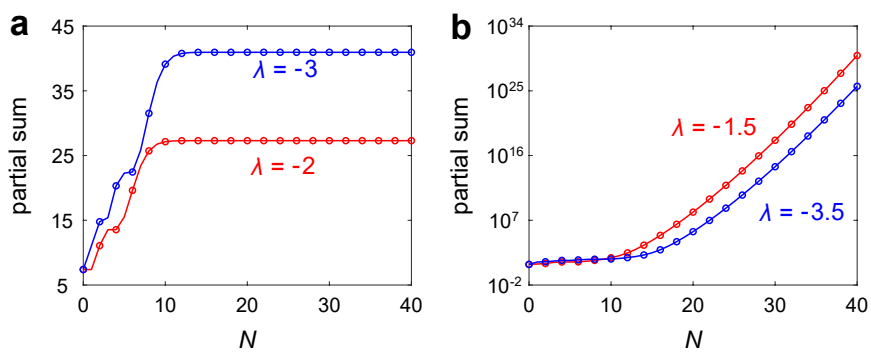

Figure 3: **Using the Hilbert space framework to determine the eigenvalues for a constitutive gene expression model**. Here the partial sum $\sum_{m=0}^{N} |\psi_m|^2/\pi_m$ of the power series $\sum_{m=0}^{\infty} |\psi_m|^2/\pi_m$ is plotted as a function of N under different choices of λ. **(a)** Partial sum $\sum_{m=0}^{N} |\psi_m|^2/\pi_m$ as a function of N for $\lambda = -2$ and $\lambda = -3$. Any $\lambda = -nd$ leads to the convergence of the power series. **(b)** Same as in (a) but for $\lambda = -1.5$ and $\lambda = -3.5$. Any $\lambda \neq -nd$ leads to the divergence of the power series. In (a) and (b), the model parameters are chosen as $s = 2$ and $d = 1$.

Appendix B A simple model of bursty protein production

Experiments have shown that many proteins are produced in a bursty manner [30], due to the rapid translation of protein from a single, short-lived mRNA molecule [31, 32]. Let G denote the gene of interest, let M denote the corresponding mRNA, and let P denote the corresponding protein. Consider the following classical two-stage model of stochastic gene expression:

$$G \xrightarrow{\rho} G + M, \quad M \xrightarrow{u} M + P, \quad M \xrightarrow{v} \varnothing, \quad P \xrightarrow{d} \varnothing, \tag{14}$$

where the first reaction describes transcription, the second reaction describes translation, and the last two reactions describe the degradation of mRNA and protein, respectively. When mRNA decays much faster compared to its protein counterpart ($\gamma = v/d \gg 1$) and when the number of protein molecules produced per mRNA lifetime ($B = u/v$) is strictly positive and bounded, it has been shown [31–33] that protein will be produced in a bursty manner. Specifically, in the limit of $\gamma \gg 1$ and $B = u/v$ is strictly positive and bounded, the two-stage model shown in Eq. (14) reduces to the following gene expression model with bursty protein synthesis and protein degradation (Fig. 2(c)):

$$G \xrightarrow{\rho p^k (1-p)} G + kP, \quad k \geq 1, \quad P \xrightarrow{d} \varnothing, \tag{15}$$

where the synthesis of protein occurs in bursts with frequency ρ and random size k sampled from a geometric distribution with parameter $p = u/(u+v) \in (0,1)$, and d is the rate of protein degradation. The microstate of the gene is described by the protein number $m = 0, 1, 2, \cdots$. The stochastic evolution of the protein number in a single cell is characterized by the Markov jump process shown in Fig. 2(d) with generator matrix

$$Q = \begin{pmatrix} -\rho p & \rho p(1-p) & \rho p^2(1-p) & \cdots \\ d & -(d+\rho p) & \rho p(1-p) & \ddots \\ & 2d & -(2d+\rho p) & \ddots \\ & & \ddots & \ddots \end{pmatrix}.$$

In steady state, it is well known that the protein number for the bursty gene expression model shown in Fig. 2(c) has the negative binomial distribution [7]

$$\pi_m = \frac{(\rho/d)_m}{m!} p^m (1-p)^{\rho/d}. \tag{16}$$

We next find all eigenvalues for bursty genes within the Hilbert space framework introduced above: if there exists a row vector $\psi = (\psi_m) \in l^2(\pi)$ such that $\psi Q = \lambda \psi$, then λ is as an eigenvalue of the generator matrix Q and ψ is the associated eigenvector. Note that the characteristic equation $\psi Q = \lambda \psi$ can be written in components as

$$(m+1)d\psi_{m+1} - (md + \rho p)\psi_m + \sum_{l=0}^{m-1} \rho p^{m-l}(1-p)\psi_l = \lambda \psi_m. \tag{17}$$

Using the generating function defined in Eq. (12), Eq. (17) can be converted into the differential equation

$$\frac{\rho p(z-1)}{1-pz} f(z) + d(1-z) f'(z) = \lambda f(z). \tag{18}$$

For convenience, we set $\psi_0 = 1$, which ensures that $f(z) = 1$. Then Eq. (18) can be solved explicitly as

$$f(z) = (1-pz)^{-\rho/d}(1-z)^{-\lambda/d}. \tag{19}$$

To find all eigenvalues of the generator matrix Q, we first focus on the case when $\lambda = -nd$ for some $n \geq 0$. In this case, $z = 1/p$ is a singular point of the generating function $f(z) = (1-pz)^{-\rho/d}(1-z)^n$ and thus the convergence radius of the power series $f(z) = \sum_{m=0}^{\infty} \psi_m z^m$ is $1/p$, which implies that

$$\overline{\lim_{m\to\infty}} \sqrt[m]{|\psi_m|} = p.$$

Hence for any $\delta > 1$, there exists $C(\delta) > 0$ such that $|\psi_m| \leq C(\delta)(p\delta)^m$ for all $m \geq 0$. Moreover, it is easy to check that $(m-1)! < (\rho/d)_m$. It then follows from Eq. (16) that

$$\begin{aligned} \sum_{m=0}^{\infty} |\psi_m|^2/\pi_m &\leq C(\delta)^2 (1-p)^{-\rho/d} \sum_{m=0}^{\infty} \frac{m!}{(\rho/d)_m} (p\delta^2)^m \\ &\leq C(\delta)^2 (1-p)^{-\rho/d} \sum_{m=0}^{\infty} m(p\delta^2)^m < \infty, \end{aligned}$$

where we have chosen $\delta > 1$ such that $p\delta^2 < 1$. This clearly show that $\psi \in l^2(\pi)$ and thus $\lambda = -nd$ is an eigenvalue.

We next focus on the case when $\lambda \neq -nd$ for all $n \geq 0$. In this case, both $z = 1$ and $z = 1/p > 1$ are singular points of $f(z) = (1-pz)^{-\rho/d}(1-z)^{-\lambda/d}$ and thus the convergence radius of the power series $f(z) = \sum_{m=0}^{\infty} \psi_m z^m$ is 1, which implies that

$$\overline{\lim_{m\to\infty}} \sqrt[m]{|\psi_m|} = 1.$$

Hence we have $\overline{\lim}_{m\to\infty} |\psi_m|\delta^m \geq 1$ for any $\delta > 1$. Moreover, it is easy to check that

$$\frac{(\rho/d)_m}{m!} \leq \frac{(\lceil \rho/d \rceil)_m}{m!} \leq (\lceil \rho/d \rceil + m - 1)^{\lceil \rho/d \rceil - 1},$$

where $\lceil x \rceil$ denotes the smallest integer that exceeds x. It then follows from Eq. (16) that

$$\begin{aligned}\overline{\lim_{m\to\infty}} |\psi_m|^2/\pi_m &\geq (1-p)^{-\rho/d} \overline{\lim_{m\to\infty}} \frac{m!}{(\rho/d)_m (p\delta^2)^m} \\ &\geq (1-p)^{-\rho/d} \overline{\lim_{m\to\infty}} \frac{1}{(\lceil \rho/d \rceil + m - 1)^{\lceil \rho/d \rceil - 1}(p\delta^2)^m} = \infty,\end{aligned}$$

where we have chosen $\delta > 1$ such that $p\delta^2 < 1$. This shows that $\psi \notin l^2(\pi)$ and thus $\lambda \neq -nd$ is not an eigenvalue.

The above analysis show that for bursty genes, all the eigenvalues of the generator matrix Q are the same as those for constitutive genes and are still given by $\lambda_n = -nd$, $n \geq 0$. To validate this, we illustrate the partial sum of the power series $\sum_{m=0}^{\infty} |\psi_m|^2/\pi_m$ for $\lambda = -nd$ and for $\lambda \neq -nd$ in Fig. 4. For the former case, the power series converges (Fig. 4(a)) and hence $\lambda = -nd$ is a true eigenvalue; for the latter case, the power series diverges (Fig. 4(b)) and hence $\lambda \neq -nd$ is not an eigenvalue.

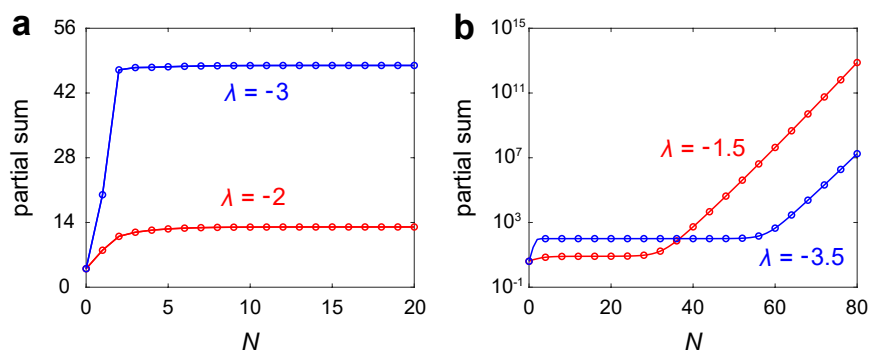

Figure 4: **Using the Hilbert space framework to determine the eigenvalues for a bursty gene expression model**. Here the partial sum $\sum_{m=0}^{N} |\psi_m|^2/\pi_m$ of the power series $\sum_{m=0}^{\infty} |\psi_m|^2/\pi_m$ is plotted as a function of N under different choices of λ. **(a)** Partial sum $\sum_{m=0}^{N} |\psi_m|^2/\pi_m$ as a function of N for $\lambda = -2$ and $\lambda = -3$. Any $\lambda = -nd$ leads to the convergence of the power series. **(b)** Same as in (a) but for $\lambda = -1.5$ and $\lambda = -3.5$. Any $\lambda \neq -nd$ leads to the divergence of the power series. In (a) and (b), the model parameters are chosen as $\rho = 2, p = 0.5, d = 1$.

Appendix C Self-repressing genes

Finally, we focus on the model studied in the main text, where the protein produced from a gene represses its own transcription, forming a negative autoregulatory gene circuit (Fig. 1(a)) [10, 19, 34]. The stochastic gene expression

dynamics is described by the Markov jump process shown in Fig. 1(b) with generator matrix

$$Q = \begin{pmatrix} Q_0 & Q_{01} & & \\ Q_{10} & Q_1 & Q_{12} & \\ & Q_{21} & Q_2 & \ddots \\ & & \ddots & \ddots \end{pmatrix},$$

where

$$Q_m = \begin{pmatrix} -(a+md) & a \\ m\nu & -[s+m(\nu+d)] \end{pmatrix}, \quad Q_{m+1,m} = \begin{pmatrix} (m+1)d & 0 \\ 0 & (m+1)d \end{pmatrix}, \quad Q_{m,m+1} = \begin{pmatrix} 0 & 0 \\ 0 & s \end{pmatrix}.$$

The spectral structure for self-repressing genes has been studied in [5, 6, 16–18]; however, the results obtained in these papers are contradictory. In our previous paper [6], we provided a complete spectrum characterization for the stochastic model of an autoregulatory feedback loop based on a complex analysis method; however, the derivation is informal because we have not proved that the eigenvectors obtained belong to the Hilbert space $l^2(\pi)$. Specifically, it is clear that $\lambda_0 = 0$ is an eigenvalue of the generator matrix Q. Furthermore, all nonzero eigenvalues are the roots of the following nontrivial continued fraction equation:

$$q = \frac{R_0 P_1}{(Q_1+q)-} \frac{R_1 P_2}{(Q_2+q)-} \frac{R_2 P_3}{(Q_3+q)-} \cdots, \tag{20}$$

where

$$R_n = -(n+1)(n+\gamma), \quad P_n = \theta + (n-1)\epsilon, \quad Q_n = n[-(n-1+\gamma) - \delta + \epsilon],$$

with

$$\begin{gathered} q = -\frac{(\lambda+d)(a+\lambda)}{d(\nu+d)} - \frac{(a+d+\lambda)\nu s}{d(\nu+d)^2}, \quad \theta = -\frac{(a+d+\lambda)\nu s}{d(\nu+d)^2}, \\ \gamma = \frac{a+\lambda}{\nu+d} + \frac{s\nu}{(\nu+d)^2}, \quad \delta = 2 + \frac{\lambda}{d}, \quad \epsilon = -\frac{\nu s}{(\nu+d)^2}. \end{gathered} \tag{21}$$

However, Ramos and coauthors have obtained different eigenvalues for the same model. In [5, 16], the authors claimed that a self-repressing gene circuit has two families of eigenvalues, i.e.

$$\lambda_{1,n} = -nd, \quad \lambda_{2,n} = -n(d+\nu) - a - \frac{s\nu}{d+\nu}, \quad n \geq 0. \tag{22}$$

A proof of this result was given in [18] using a linear algebraic method. In particular, the eigenvalues given in [5, 16] are all real. We now show that the linear algebraic method proposed in [18] is questionable. In [18], the author investigated the eigenvalues of the matrix

$$U_s = \mathrm{diag}(L, L, \cdots) Q^T \mathrm{diag}(L, L, \cdots)^{-1}, \tag{23}$$

with

$$L = \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix}.$$

A matrix V was then constructed such that

$$V U_s = \Lambda V, \tag{24}$$

for some diagonal matrix Λ. It was then claimed that the diagonal elements of Λ are all eigenvalues of U_s and hence are also all eigenvalues of the generator matrix Q (note that U_s and Q^T are the same up to a similar transformation and they have the same eigenvalues). Note that U_s and Λ can be represented in block form as

$$U_s = \begin{pmatrix} LQ_0^T L^{-1} & LQ_{10}^T L^{-1} & & \\ LQ_{01}^T L^{-1} & LQ_1^T L^{-1} & LQ_{21}^T L^{-1} & \\ & LQ_{12}^T L^{-1} & LQ_2^T L^{-1} & \ddots \\ & & \ddots & \ddots \end{pmatrix}, \quad \Lambda = \begin{pmatrix} \Lambda_0 & & & \\ & \Lambda_1 & & \\ & & \Lambda_2 & \\ & & & \ddots \end{pmatrix},$$

where Λ_n, $n \geq 0$ are 2×2 matrices. Moreover, the matrix V can be represented in block form as

$$V = \begin{pmatrix} V_{00} & V_{01} & V_{02} & \cdots \\ V_{10} & V_{11} & V_{12} & \cdots \\ V_{20} & V_{21} & V_{22} & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix},$$

where V_{mn}, $m, n \geq 0$ are also 2×2 matrices. From the condition $VU_s = \Lambda V$, we obtain the equation

$$V_{m,n-1}U_{n-1,n} + V_{mn}U_{nn} + V_{m,n+1}U_{n+1,n} = \Lambda_m V_{mn}, \quad \forall m, n \geq 0, \tag{25}$$

where

$$U_{n-1,n} = LQ_{n,n-1}^T L^{-1}, \quad U_{nn} = LQ_n^T L^{-1}, \quad U_{n+1,n} = LQ_{n,n+1}^T L^{-1}.$$

Note that V_{mn}, L, and Λ_n are 2×2 matrices. Set

$$V_{mn}L = \begin{pmatrix} v_{(0,m),(0,n)} & v_{(0,m),(1,n)} \\ v_{(1,m),(0,n)} & v_{(1,m),(1,n)} \end{pmatrix}, \quad \Lambda_n = \begin{pmatrix} \lambda_{0,n} & \\ & \lambda_{1,n} \end{pmatrix}.$$

Then Eq. (25) can be written in component form as

$$\begin{aligned} &mdv_{(i,n),(0,m-1)} - (a + md)v_{(i,n),(0,m)} + av_{(i,n),(1,m)} = \lambda_{i,n}v_{(i,n),(0,m)}, \\ &mdv_{(i,n),(1,m-1)} + m\nu v_{(i,n),(0,m)} - [s + m(\nu + d)]v_{(i,n),(1,m)} + sv_{(i,n),(1,m+1)} = \lambda_{i,n}v_{(i,n),(1,m)}, \end{aligned} \tag{26}$$

where $v_{(i,n),(0,-1)} = v_{(i,n),(1,-1)} = 0$ by default. For convenience, we set $v_{(i,n),(0,0)} = 1$. It is clear that

$$v_{(i,n),(1,0)} = (1 + \lambda_{i,n}/a)v_{(i,n),(0,0)}.$$

Solving Eq. (26) recursively yields that for any $n, m \geq 0$ and $i = 0, 1$,

$$\begin{aligned} v_{(i,n),(1,m+1)} &= \frac{[s + m(\nu + d) + \lambda_{i,n}]v_{(i,n),(1,m)} - n\nu v_{(i,n),(0,m)} - mdv_{(i,n),(1,m-1)}}{s}, \\ v_{(i,n),(0,m+1)} &= \frac{av_{(i,n),(1,m+1)} + (m+1)dv_{(i,n),(0,m)}}{a + (m+1)d + \lambda_{i,n}}. \end{aligned}$$

This implies that the matrix $V_{mn}L$ can be determined recursively. Then V_{mn} can be constructed as

$$V_{mn} = \begin{pmatrix} v_{(0,m),(0,n)} & v_{(0,m),(1,n)} \\ v_{(1,m),(0,n)} & v_{(1,m),(1,n)} \end{pmatrix} L^{-1}.$$

The above computations show that, regardless of how the diagonal matrix Λ is chosen, one can always find a matrix V such that $VU_s = \Lambda V$. Hence even if $VU_s = \Lambda V$ holds, we cannot conclude that the diagonal elements of Λ are all eigenvalues of the generator matrix Q.

We next apply the Hilbert space framework introduced above to find the correct eigenvalues for self-repressing genes: if there exists a row vector $\psi = (\psi_{i,m}) \in l^2(\pi)$ such that $\psi Q = \lambda\psi$, then λ is as an eigenvalue of the generator matrix Q and ψ is the associated eigenvector. It is clear that $\lambda_0 = 0$ is an eigenvalue of the generator matrix Q. We now prove that the solutions of Eq. (20) give all nonzero eigenvalues of Q. Note that the characteristic equation $\psi Q = \lambda\psi$ can be written in components as

$$\begin{aligned} &(m+1)d\psi_{0,m+1} + m\nu\psi_{1,m} - (a+md)\psi_{0,m} = \lambda\psi_{0,m}, \\ &s\psi_{1,m-1} + (m+1)d\psi_{1,m+1} + a\psi_{0,m} - [s + m(\nu+d)]\psi_{1,m} = \lambda\psi_{1,m}, \end{aligned} \tag{27}$$

where $\psi_{1,-1} = 0$ by default. To proceed, we define two generating functions

$$f_i(z) = \sum_{m=0}^{\infty} \psi_{i,m} z^m, \quad i = 0, 1, \tag{28}$$

and let $f(z) = f_0(z) + f_1(z)$ be the total generating function. In [6], by using a complex analysis method, we have shown that the total generating function f can be computed in closed form as

$$f(z) = (z-1)Hc\left(q, \theta, \gamma, \delta, \epsilon; \frac{\nu+d}{\nu}(z - z_0)\right), \tag{29}$$

and the generating functions f_0 and f_1 can be computed exactly as

$$f_1 = \frac{1}{s(z-1)}[\lambda f - d(1-z)\partial_z f], \quad f_0 = f - f_1, \tag{30}$$

where $Hc(z)$ is the local confluent Heun function [35, 36], and $q, \theta, \gamma, \delta, \epsilon$ are the parameters given in Eq. (21). Hence, from Eq. (28), $\psi_{0,m}$ and $\psi_{1,m}$ can be recovered from the generating functions as

$$\psi_{i,m} = \frac{1}{m!} f_i^{(m)}(z)\Big|_{z=0}, \quad i = 0, 1. \tag{31}$$

To simplify, in what follows, we abbreviate $Hc(q, \theta, \gamma, \delta, \epsilon; z)$ as $Hc(z)$. Before giving the rigorous proof, we recall that the local confluent Heun function has the following important properties [35, 36]:

(i) If λ is a solution of Eq. (20), then $Hc(z)$ is holomorphic over whole complex plane. In this case, the local confluent Heun function is called a confluent Heun function. Let $Hc(z) = \sum_{l=0}^{\infty} c_l z^l$ be the power series expansion of the confluent Heun function. Then the convergence radius of $Hc(z) = \sum_{l=0}^{\infty} c_l z^l$ is ∞. Moreover, there exists $\kappa > 0$ such that $c_l \leq \kappa^l / l!$.

(ii) If λ is not a solution of Eq. (20), then $Hc(z)$ has only one singularity at $z = 1$ and the convergence radius of the power series $Hc(z) = \sum_{l=0}^{\infty} c_l x^l$ is 1.

We first focus on the case where λ is a solution to Eq. (20). In this case, we have

$$\begin{aligned} \left|\partial_z^m Hc\left(-\frac{\nu+d}{\nu}z_0\right)\right| &= \left|\sum_{l=m}^{\infty} c_l \left(\frac{\nu+d}{\nu}\right)^l \frac{l!}{(l-m)!}(-z_0)^{l-m}\right| \\ &\leq \left(\frac{\nu+d}{\nu}\kappa\right)^m \sum_{l=m}^{\infty} \frac{1}{(l-m)!}\left(\frac{\nu+d}{\nu}\kappa z_0\right)^{l-m} \\ &= \left(\frac{\nu+d}{\nu}\kappa\right)^m \exp\left(\frac{\nu+d}{\nu}\kappa z_0\right). \end{aligned}$$

Hence, it is easy to see that there exist two positive constants M and η such that

$$\begin{aligned}\frac{1}{m!}\left|f^{(m)}(0)\right| &= \frac{1}{m!}\left|m\partial_z^{m-1}Hc\left(-\frac{\nu+d}{\nu}z_0\right)-\partial_z^m Hc\left(-\frac{\nu+d}{\nu}z_0\right)\right| \\ &\le M\frac{\eta^m}{(m-1)!}.\end{aligned}$$

Similarly, it follows from Eqs. (30) and (31) that

$$\begin{aligned}|\psi_{0,m}| &= \frac{1}{m!}\left|f_0^{(m)}(0)\right| \le M\frac{\eta^m}{(m-1)!}, \\ |\psi_{1,m}| &= \frac{1}{m!}\left|f_1^{(m)}(0)\right| \le M\frac{\eta^m}{(m-1)!}.\end{aligned} \tag{32}$$

On the other hand, recall the following property of the confluent hypergeometric function [37]:

$${}_1F_1(\alpha+m;\beta+m;-wz_0) = e^{-wz_0}(1+o(1)), \quad m\to\infty. \tag{33}$$

Hence, it follows from Eqs. (4) and (33) that

$$\begin{aligned}\pi_{1,m} &= \frac{d}{\nu+d}e^{\alpha-\beta}\frac{\beta^{\beta-1}}{\alpha^{\alpha-1}}e^{-wz_0}\frac{m^{\alpha-\beta}w^m}{m!}(1+o(1)), \\ \pi_{0,m} &= \frac{\nu}{\nu+d}e^{\alpha-\beta}\frac{\beta^{\beta-1}}{\alpha^{\alpha-1}}e^{-wz_0}\frac{m^{\alpha-\beta}w^m}{m!}(1+o(1)).\end{aligned} \tag{34}$$

This indicates that $\pi_{i,m} \ge \sigma m^{\alpha-\beta}w^m/m!$ for some constant $\sigma > 0$. It then follows from Eq. (32) that

$$\sum_{i=0}^{1}\sum_{m=0}^{\infty}|\psi_{i,m}|^2/\pi_{i,m} \le \frac{2M^2}{\sigma}\sum_{m=0}^{\infty}\frac{m^{1-\alpha+\beta}(\eta^2/w)^m}{(m-1)!} < \infty.$$

This show that $\psi = (\psi_{i,m}) \in l^2(\pi)$ and thus the roots of the continued fraction equation given in Eq. (20) are indeed the eigenvalues of the generator matrix Q.

We next focus on the case where λ is not a solution of Eq. (20). From Eq. (29), the convergence radius of the power series

$$f(z) = \sum_{m=0}^{\infty}(\psi_{0,m}+\psi_{1,m})z^m$$

is the same as that of $Hc((\nu+d)(z-z_0)/\nu) = \sum_{l=0}^{\infty} b_l z^l$. Since $Hc(z)$ has only one singularity at $z=1$, it is clear that $Hc((\nu+d)(z-z_0)/\nu)$ has only one singularity at $z = z_0+\nu/(\nu+d) = 1$. Thus the convergence radius of $f(z)$ must be 1. Then we immediately obtain

$$\overline{\lim_{m\to\infty}}\sqrt[m]{|\psi_{i,m}|} \ge 1, \quad i=0,1.$$

Hence we have $\overline{\lim}_{m\to\infty}|\psi_{i,m}|\sigma^m \ge 1$ for any $\sigma > 1$. It follows from Eq. (34) that $\pi_{i,m} \le M' m^{\alpha-\beta}w^m/m!$ for some constant $M' > 0$. This indicates that

$$\overline{\lim_{m\to\infty}}|\psi_{i,m}|^2/\pi_{i,m} \ge \frac{1}{M'}\overline{\lim_{m\to\infty}}\frac{m!}{m^{\alpha-\beta}\sigma^{2m}w^m} = \infty.$$

This shows that $\psi = (\psi_{i,m}) \notin l^2(\pi)$ and thus any complex number that is not the solution of Eq. (20) is also not an eigenvalue of the generator matrix Q. Using the Hilbert space framework, we have rigourously proved that the eigenvalues obtained in [6] are correct and can be complex numbers, while the real ones obtained in [5, 16–18] are incorrect.

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