NO-OSCILLATION THEOREM FOR THE TRANSIENT DYNAMICS OF THE LINEAR SIGNAL TRANSDUCTION PATHWAY AND BEYOND

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Abstract. Understanding the connection between the topology of a biochemical reaction network and its dynamical behavior is an important topic in systems biology. We proved a no-oscillation theorem for the transient dynamics of the linear signal transduction pathway, that is, there are no dynamical oscillations for each species if the considered system is a simple linear transduction chain equipped with an initial stimulation. In the nonlinear case, we showed that the no-oscillation property still holds for the starting and ending species, but oscillations generally exist in the dynamics of intermediate species. We also discussed different generalizations on the system setup. The established theorem will provide insights on the understanding of network motifs and the choice of mathematical models when dealing with biological data.

1. Introduction. Modelling biochemical systems with reaction networks is always a fundamental and challenging task in systems biology. To explain the observed phenomenon in biological experiments, the researcher proposes new or refine existing theoretical models to achieve qualitative, or even quantitative agreements with the available experimental data. One common modelling approach is by deterministic, or stochastic ordinary differential equations to study the interested dynamics [7, 11]. Typical theoretical tools include local stability analysis, bifurcation analysis or sensitivity analysis when the dynamical system is parameter dependent [5, 16].

It is an interesting and important problem to understand the connection between the topology of a biochemical reaction network and its dynamical behavior. One classical reference on this topic is [1], in which some simple and fundamental biochemical reaction circuits are proposed to achieve desired biological functions. The oscillation dynamics is typically discussed in [6] when the delay is involved in the considered dynamical system. In [13], a massive search in the 3-node network configuration and parameter space is performed to find the robust biological circuits which can achieve the adaptation function. How to generalize such strategy to more
complex systems is still an issue in future research. Compared with these biophysical and numerical approaches in exploring the relation between the topology and dynamical behavior, mathematically, it is also desirable to rigorously analyze the dynamical pattern for specially structured systems. Such type of results will give more solid and thorough understanding on the reaction dynamics than mere numerical investigations. A classical result on this point is the deficiency zero/one theorem and its ramifications concerning the relation between the asymptotic behavior of a chemical reaction network and its topological structure [3, 4, 5, 8, 18].

Motivated by the mathematical modelling for the interactions between epidermal growth factor receptors (EGFRs) and Src family kinases in cancer research [2, 15], we formulated and proved a no-oscillation theorem for the transient dynamics of the linear signal transduction pathway in this paper. To be more specific, for the following linear chain reaction scheme (1)

$$
\begin{align*}
S_1 & \xrightarrow{\gamma_1, \mu_2} S_2 & \xrightarrow{\gamma_2, \mu_3} \cdots & \xrightarrow{\gamma_{N-1}, \mu_N} S_N, \\
\downarrow \sigma_1 & \quad \downarrow \sigma_2 & \quad \downarrow \sigma_N & \\
0 & \quad 0 & \quad 0 &
\end{align*}
$$

(1)

where $\gamma_i$, $\mu_i$ and $\sigma_i$ are corresponding reaction rate functions. If all reactions are first order mass reaction, the ODEs are linear, we can show that there are no dynamical oscillations for each species if the above system is equipped with a single initial stimulation, i.e. with initial state

$$q|_{t=0} = (1, 0, \ldots, 0)^T, \quad (2)$$

where $q = (q_1, q_2, \ldots, q_N)^T$ and $q_i$ represents the concentration of species $S_i$. Denote by $\#\{A\}$ the number of elements in set $A$. Our main theorem can be stated as follows.

**Theorem 1** (No-oscillation theorem). For linear system (3) with the condition $\gamma_i, \mu_i > 0$ and $\sigma_j \geq 0$ for any $i$, $\sum_{j=1}^N \sigma_j > 0$, and the initial value (2), there are no oscillations in the overall dynamics of $q$, i.e. $\dot{q}_i(t) < 0$ for any $t \geq 0$; $\#\{t : t > 0, \dot{q}_i(t) = 0\} \leq 1$ for $2 \leq i \leq N$. Furthermore, we have $\lim_{t \to \infty} q_i(t) = 0$ for $i = 1, 2, \ldots, N$.

The condition of the above theorem can be relaxed (see Section 2.2). For nonlinear reaction rate functions in biochemical reactions, we find that the no-oscillation property still holds for the species $S_1$ and $S_N$, but oscillation can occur in the dynamics of $q_i$ for $i = 2, \ldots, N - 1$. This is summarized in the following theorem.

**Theorem 2**. For nonlinear system (20) with initial value (2) and Assumptions 3-4 (see Section 3) on the nonlinear rates $\gamma_i(x)$, $\mu_i(x)$ and $\sigma_i(x)$, we have $\dot{q}_i(t) < 0$ for any $t \geq 0$; $\#\{t : t > 0, \dot{q}_N(t) = 0\} = 1$ and $\lim_{t \to \infty} q_i(t) = 0$ for $i = 1, 2, \ldots, N$. That is, there are no oscillations in the overall dynamics of $q_1$ and $q_N$.

Similar results are also generalized to the signal transduction pathways with branching structure in a slightly modified form (see Theorems 5 and 6 in Section 4).

We would like to mention that most of previous analysis on reaction dynamics mainly focuses on the limiting behavior, e.g. the local stability of attractors as $t \to \infty$. There are very few mathematical results concerning the transient behavior of a dynamical system. A related work, but with different focus, concerns the overshoot phenomena for non-equilibrium dynamics [10]. Our analysis reveals that the oscillation behavior can not appear in the transient process of a simple
network topology like the linear signal transduction chain, which mathematically builds a connection between the network structure and its functional outcome. The established theorem will provide insights on the understanding of network motifs and choice of mathematical models when dealing with biological data. Indeed, this no-oscillation theorem has been utilized to rule out some candidate models in our recent mathematical modeling for EGFR/PDGFR signaling pathway based on the experimental data.

We need to point out that our no-oscillation theorem is different from the classical deficiency zero theorem although formally both theorems indicate that no oscillations exist in the trajectory. In fact, they are concerned about completely different aspects of the solution of a reaction network. The deficiency zero theorem tells us about the asymptotic or limiting behavior of the solution when $t \to \infty$: that is, a deficiency-zero reaction system admits at most one positive steady state and no positive cyclic composition trajectory in the sense that $q(0) = q(T)$ for some $T > 0$. However, our no-oscillation theorem is concerned about the transient behavior of the solution of a signal transduction pathway equipped with the single stimulation initial: that is, for the simple linear signal transduction chain (1), its transient dynamics approaching the unique stable point can only be of the single peak pattern instead of an oscillatory decay. In this simplest setup, our no-oscillation theorem is an enhancement of the deficiency zero theorem on further claiming about the transients. The conceptual difference between our no-oscillation theorem and the deficiency zero theorem is also illustrated in Example 2 in Sec. 3.

\[ \text{(a) Simplified MAPK signaling cascade pathway.} \]

\[ \text{(b) Motif in the planar cell polarity WNT signaling pathway.} \]

\textbf{Figure 1.} (a). Illustration of a simplified MAPK signaling cascade. Here Raf}^p, \text{MEK}^p \text{and ERK}^p \text{represent the phosphorylated protein kinase. (b). Part of planar cell polarity WNT signaling pathway.}

It is also necessary to remark that although generally a full signal transduction pathway may be extremely complex, the considered reaction pathway in this paper is quite common as simple motifs of a complex biological circuit. We illustrate this point in Fig. 1 for MAPK and WNT signaling pathways [12]. In the simplified MAPK signaling cascade system (Fig. 1(a)), the growth factor (GF) acts as an initial signal and each stage in the cascade system is a linear signal transduction unit. In the planar cell polarity WNT signaling pathway (Fig. 1(b)), the signal transduction from WNT to Rho and its downstream protein is of similar type. So
the proved theorem can be applied to these motifs and helps to gain understanding of the system dynamics.

The rest of this paper is organized as follows. In Section 2, we give the complete analysis on the no-oscillation property of the solution of linear systems. In Section 3, we provide a qualitative analysis on the dynamical behavior of the solution of nonlinear systems and present the counter-example for general cases. Then we consider the generalization of the network structure to branching case in Section 4. In Section 5, we give a brief summary.

2. Linear system. In this section, we will prove the no-oscillation theorem for the linear chain reaction scheme (1) with the following ODEs by the law of mass action

\[
\begin{pmatrix}
\dot{q}_1 \\
\dot{q}_2 \\
\vdots \\
\dot{q}_{N-1} \\
\dot{q}_N
\end{pmatrix} =
\begin{pmatrix}
-\gamma_1 - \sigma_1 & \mu_2 & \cdots & 0 \\
\gamma_1 & -\gamma_2 - \mu_2 - \sigma_2 & \cdots & 0 \\
0 & 0 & \cdots & 0 \\
0 & 0 & \cdots & -\mu_N - \sigma_N
\end{pmatrix}
\begin{pmatrix}
q_1 \\
q_2 \\
\vdots \\
q_{N-1} \\
q_N
\end{pmatrix},
\]  

(3)

where \( q_i(t) \) denotes the concentration of species \( S_i \) at time \( t \). We assume the initial condition (2). The solution \( q \) also has probabilistic interpretation that it gives the probability distribution of a \( Q \)-process with \( N + 1 \) states \( \{ S_1, \ldots, S_N, \emptyset \} \) by setting the empty set \( \emptyset \) as an absorbing state when the transition starts from state \( S_1 \) [14].

We will simply denote the system (3) by

\[
\dot{q} = Aq, \quad q|_{t=0} = (1, 0, \ldots, 0)^T,
\]  

(4)

where \( A \) is the corresponding coefficient matrix. The above system has an equivalent formulation

\[
\dot{q} = Aq + \delta(t)e_1, \quad q|_{t=0} = (0, 0, \ldots, 0)^T,
\]  

(5)

where \( \delta(t) \) is the Dirac delta function and \( e_1 = (1, 0, \ldots, 0)^T \). It can be interpreted as the system response to a unit stimulation signal exerted to species \( S_1 \) when the system is at rest state initially.

We classify the linear systems according to the following two assumptions.

**Assumption 1 (Non-degenerate case).** For any \( i, \gamma_i > 0, \mu_i > 0, \sigma_i \geq 0 \) and \( \sum_{i=1}^{N} \sigma_i > 0 \).

**Assumption 2 (Degenerate case).** For any \( i, \gamma_i \geq 0, \mu_i \geq 0, \sigma_i \geq 0 \) and \( 0 \in \{ \gamma_1, \ldots, \gamma_{N-1}, \mu_2, \ldots, \mu_N, \sum_{i=1}^{N} \sigma_i \} \).

In the non-degenerate case, the condition \( \sum_{i=1}^{N} \sigma_i > 0 \) ensures the decay of the total mass, which simplifies the proof. The degeneracy means that at least one of the reversible reaction channel in the backbone is closed or all of the decay reactions disappear. We will demonstrate that the degenerate case can be handled by a continuation argument based on the result for the non-degenerate case.

The proof of the linear non-degenerate case is accomplished by several major steps. First we analyze the eigenvalues of the matrix \( A \) and derive the explicit formula of the solution by an exponential sum, whose coefficients are also characterized. We then introduce the key tool, the sign change function, and bound the number of real roots of an exponential sum by its sign change function. This result is utilized to give an upper bound of the number of critical points in the transient dynamics. Finally we establish the desired theorem by specially taking into account the multiplicity of critical points at \( t = 0 \).
2.1. Non-degenerate case. At first let us present some preliminary results about the matrix $A$.

**Proposition 1.** The eigenvalues of $A$ are real and negative.

*Proof.* Let $D = \text{diag}\{d_1, d_2, \ldots, d_N\}$. Define $B = D^{-1} A D$. As $A$ is tridiagonal and its off-diagonal elements $a_{i,i+1} = \mu_i + 1, a_{i+1,i} = \gamma_i$ has the same sign, we obtain that $B$ is also tridiagonal and

$$\frac{b_{i,i+1}}{b_{i+1,i}} = \frac{d_{i+1}^2 \mu_{i+1}}{d_i^2 \gamma_i}, \quad i = 1, 2, \ldots, N - 1.$$ 

Let

$$d_1 = 1, \quad \frac{d_{i+1}}{d_i} = \sqrt{\frac{\gamma_i}{\mu_{i+1}}}, \quad i = 1, 2, \ldots, N - 1,$$ 

then $B$ is a symmetric matrix. So we have $\lambda(A) = \lambda(B) \in \mathbb{R}$.

Since $A$ is an irreducibly, diagonally dominant matrix [9], we have $\det(A) \neq 0$. Taking advantage of the fact that the column sums of $A$ are all non-positive and at least one of them is negative, say $\sigma_{i_0} > 0$ for some $i_0$, we have

$$|\lambda + \gamma_{i_0} + \mu_{i_0} + \sigma_{i_0}| \leq \mu_{i_0} + \gamma_{i_0}$$

for any eigenvalue $\lambda$ of $A$ by the Gershgorin circle theorem [9]. So we get

$$\lambda \leq -\sigma_{i_0} < 0.$$ 

The proof is completed. \(\square\)

**Proposition 2.** The eigenvalues of $A$ are distinct.

*Proof.* Assume that $\lambda$ is an eigenvalue of $A$. First we prove that

$$\dim(\text{Null}(\lambda I - A)) = 1,$$ 

where $\text{Null}(\cdot)$ means the null space of a matrix. As $\lambda$ is an eigenvalue of $A$, we have $\dim(\text{Null}(\lambda I - A)) \geq 1$. To prove that $\dim(\text{Null}(\lambda I - A)) \leq 1$, let us consider the bottom left $(N - 1) \times (N - 1)$ submatrix of $\lambda I - A$, i.e.

$$
\begin{pmatrix}
-\gamma_1 & \lambda + \gamma_2 + \mu_2 + \sigma_2 & -\mu_3 & \cdots & 0 \\
0 & -\gamma_2 & \lambda + \gamma_3 + \mu_3 + \sigma_3 & \cdots & 0 \\
0 & 0 & -\gamma_3 & \cdots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & \cdots & -\gamma_{N-1}
\end{pmatrix}.
$$

Since $\gamma_i \neq 0$ for any $i$, this submatrix is of full rank. Thus we obtain

$$\dim(\text{Null}(\lambda I - A)) \leq 1,$$

which implies that the geometric multiplicity of eigenvalue $\lambda$ is 1.

According to the proof of Proposition 1, $A$ is similar to a symmetric matrix. Due to the fact that the geometric and algebraic multiplicity is the same for a symmetric matrix, we get the desired result. \(\square\)

As a conclusion of Propositions 1 and 2, the eigenvalues of $A$, or $B$, can be listed as:

$$0 > \lambda_1 > \lambda_2 > \cdots > \lambda_N.$$ 

Denote the corresponding normalized right eigenvectors of $B$ by $u_i$, i.e.

$$Bu_i = \lambda_i u_i, \quad \|u_i\| = 1, \quad i = 1, 2, \ldots, N,$$ 

(8)
where $u_i = (u_{1i}, u_{2i}, \ldots, u_{Ni})^T$. We have that $\{u_i\}_{i=1,2,\ldots,N}$ forms an orthonormal basis of $\mathbb{R}^N$, and

$$A = DBD^{-1} = DUU^TD^{-1},$$

(10)

where $U = (u_1, u_2, \ldots, u_N)$, $\Lambda = \text{diag}(\lambda_1, \lambda_2, \ldots, \lambda_N)$. Correspondingly, the right eigenvectors of $A$ have the form

$$Av_i = \lambda_i v_i, \quad v_i = Du_i, \quad i = 1, 2, \ldots, N.$$

(11)

The solution of Eq. (4) can be represented by matrix exponential as

$$q(t) = e^{At}q(0) = \sum_{j=1}^{N} e^{\lambda_j t} Du_j u_j^T D^{-1} q(0)$$

$$= d_1^{-2} \sum_{j=1}^{N} e^{\lambda_j t} v_{1j} = \sum_{j=1}^{N} e^{\lambda_j t} v_{1j} v_j$$

(12)

by the fact that $d_1 = 1$ and $q(0) = e_1$. In component form, we have

$$q_i(t) = \sum_{j=1}^{N} \alpha_{ij} e^{\lambda_j t}, \quad \alpha_{ij} = v_{ij} v_{1j}.$$  

(13)

Simple observation shows that the system approaches $(0, 0, \ldots, 0)$ as $t \to \infty$ since $\lambda_i < 0$ for any $i$. Especially, we have that $q_1(t)$ monotonically decreases to zero since $\alpha_{1j} = v_{1j}^2 \geq 0$.  

(14)

To further analyze the oscillatory behavior of $q(t)$, we need to understand more about the coefficients $\alpha_{ij}$ in $q_i(t)$.

**Lemma 1.** Denote by $A_i$ the upper-left $i \times i$ submatrix of $A$. We have

$$v_{ij} = \frac{\det(\lambda_j I - A_{i-1})}{\prod_{k=2}^{i} \mu_k} v_{1j}, \quad i = 2, 3, \ldots, N; \quad j = 1, 2, \ldots, N.$$  

(15)

**Proof.** Prove by induction. For $N = 2$, we have

$$\begin{pmatrix} \lambda_j + \gamma_1 + \sigma_1 & -\mu_2 \\ -\gamma_1 & \lambda_j + \mu_2 + \sigma_2 \end{pmatrix} \begin{pmatrix} v_{1j} \\ v_{2j} \end{pmatrix} = 0, \quad j = 1, 2.$$

Solve the first equation, we get

$$v_{2j} = \frac{\lambda_j + \gamma_1 + \sigma_1}{\mu_2} v_{1j}.$$  

Assume that the lemma holds for the order of matrix $n < N$, $N \geq 3$. Let us prove for $n = N$. Note that $A_i$ has the same structure as $A$, so we only need to prove that (15) holds for $v_{Ni}$. The $(N-1)$-th equation of $(\lambda_j I - A)v_j = 0$ gives

$$-\gamma_{N-2} v_{N-2j} + (\lambda_j + \gamma_{N-1} + \mu_{N-1} + \sigma_{N-1}) v_{N-1j} - \mu_N v_{Nj} = 0.$$
Proof. The case Corollary 3. We obtain

\[
v_{Nj} = \frac{1}{\mu_N} \left( (\lambda_j + \gamma_{N-1} + \mu_{N-1} + \sigma_{N-1})v_{N-1,j} - \gamma_{N-2}v_{N-2,j} \right)
\]

\[
= \frac{v_{1j}}{\prod_{k=2}^{N} \mu_k} \left( (\lambda_j + \gamma_{N-1} + \mu_{N-1} + \sigma_{N-1}) \det(\lambda_j I - A_{N-2}) \right.
\]

\[
- \gamma_{N-2} \mu_{N-1} \det(\lambda_j I - A_{N-3}) \right)
\]

\[
= \frac{\det(\lambda_j I - A_{N-1})}{\prod_{k=2}^{N} \mu_k} v_{1j}
\]

by induction assumption, where we take the convention \(\det(\lambda_j I - A_{N-3}) = 1\) in the third row if \(N = 3\).

Now we have the explicit formula for each \(v_{ij}\). We then investigate an important order parameter related to the oscillatory behavior, the sign changes of the coefficients \(\alpha_{ij}\) in \(q_i(t)\).

**Definition 1** (Sign change function). Let \(c = (c_1, c_2, \ldots, c_N)\). Assume \(\lambda_1 > \lambda_2 > \ldots > \lambda_N\) and \(\|c\| \neq 0\). For a function \(f(t) = \sum_{i=1}^{N} c_i e^{\lambda_i t}\) with \(c_i \neq 0\) for \(i = 1, 2, \ldots, N\), we define the sign change function of \(f\) by the number of sign changes of \(c\), i.e.

\[
sc(f) = sc(c) = \sum_{i=1}^{N-1} |\text{sgn}(c_{i+1}) - \text{sgn}(c_i)|/2,
\]

where \(\text{sgn}(x) = 1\) if \(x > 0\), and \(-1\) otherwise. If some of \(c_i\) are 0 in \(c\), we define

\[
sc(f) = sc(c) = sc(\hat{c}),
\]

where \(\hat{c}\) is formed by dropping the zero components in \(c\).

**Example 1.** \(sc(1, -1, -1, -1, 1, -1) = 4\), \(sc(1, 0, -1, 0, -1, 1) = 2\), \(sc(0, 1) = 0\).

**Corollary 1.** \(sc(q_i) = sc(q_i^{(k)})\) for \(i = 1, 2, \ldots, N\), \(k \in \mathbb{N}\).

It is straightforward by direct calculation. Moreover, we have the following corollaries from Lemma 1.

**Corollary 2.** \(v_{1j} \neq 0\) for \(j = 1, 2, \ldots, N\).

*Proof.* Otherwise the eigenvector \(v_j = 0\), which is a contradiction. \(\square\)

**Corollary 3.** \(sc(q_i) \leq i - 1\) for \(i = 1, 2, \ldots, N\).

*Proof.* The case \(i = 1\) is trivial. By (13) and (15), we have

\[
sc(q_i) = sc(\alpha_{i1}, \alpha_{i2}, \ldots, \alpha_{iN})
\]

\[
= sc(v_{1i}v_{11}, v_{2i}v_{11}, \ldots, v_{Ni}v_{1N})
\]

\[
= sc(\det(\lambda_j I - A_{i-1}) - \gamma_{N-2}v_{N-2,j} \prod_{k=2}^{N} \mu_k)
\]

\[
= sc(\det(\lambda_1 I - A_{i-1}), \det(\lambda_2 I - A_{i-1}), \ldots, \det(\lambda_N I - A_{i-1}))
\]

(17)

Define a polynomial of degree \(i - 1\)

\[
p(\lambda) = \det(\lambda I - A_{i-1})
\]

For each sign change in \((p(\lambda_1), p(\lambda_2), \ldots, p(\lambda_N))\), without loss of generality, say \(p(\lambda_1)p(\lambda_2) < 0\), there exists \(\lambda_1 > \lambda > \lambda_2\) such that \(p(\lambda) = 0\). According to the
fundamental theorem of algebra, there are at most $i - 1$ roots of $p(\lambda)$, so there are at most $i - 1$ sign changes in $q_i$. Thus we obtain

$$\text{sc}(q_i) = \text{sc}(p(\lambda_1), p(\lambda_2), \ldots, p(\lambda_N)) \leq i - 1.$$ 

The proof is done. \qed

**Lemma 2.** Assume $\lambda_1 > \lambda_2 > \cdots > \lambda_N$ and $\|c\| \neq 0$. Denote by $r(f)$ the number of real roots of $f(t) = \sum_{i=1}^{N} c_i e^{\lambda_i t}$ (counting multiplicities). We have $r(f) \leq \text{sc}(f)$.

**Proof.** Prove by induction. For $N = 1$, there are no real roots of $f(t) = c_1 e^{\lambda_1 t}$, so we have $r(f) = 0 \leq 0 = \text{sc}(f)$. Assume that the lemma holds for $(N - 1)$-term summation case, $N \geq 2$. Now we prove for the $N$-term case.

If $c_i = 0$ for some $i$, the answer is trivial by induction. Assume that $c_i \neq 0$ for any $i$ in the following proof. Define

$$k = \max\{i : c_j c_1 > 0 \text{ for } 1 \leq j \leq i\}.$$ 

Rewrite

$$f(t) = e^{\lambda_k t} \left( c_k + \sum_{i \neq k} c_i e^{(\lambda_i - \lambda_k)t} \right)$$

and denote $g(t) = c_k + \sum_{i \neq k} c_i e^{(\lambda_i - \lambda_k)t}$. We have

$$\dot{g}(t) = \sum_{i \neq k} c_i (\lambda_i - \lambda_k) e^{(\lambda_i - \lambda_k)t}.$$ 

Now we estimate the sign changes of $\dot{g}(t)$. We note that the coefficients of $\dot{g}(t)$ have the same sign to that of $f(t)$ in the first $k - 1$ terms, and the opposite sign to that of $f(t)$ in the last $N - k$ terms. According to the choice of $k$, the sign change is 1 for $f(t)$ in the first $k + 1$ terms but 0 for $\dot{g}(t)$ in the first $k$ terms, and the coefficients of $\dot{g}$ and $f$ have the same sign in the remaining $N - k$ terms. We thus obtain

$$\text{sc}(\dot{g}) - \text{sc}(f) = -1.$$ 

Applying the induction assumption, we have $r(\dot{g}) \leq \text{sc}(\dot{g}) = \text{sc}(f) - 1$. By Rolle’s theorem, we have

$$r(g) \leq r(\dot{g}) + 1 \leq \text{sc}(f)$$

by counting multiplicities of roots. Finally, we obtain

$$r(f) = r(g) \leq \text{sc}(f).$$

The induction is complete. \qed

The following properties of the solution $q$ of Eq. (4) are essential.

**Proposition 3.** For $k \in \mathbb{N}$, $q_{i}^{(k)}(0) = 0$ for $i \geq k + 2$.

**Proof.** Prove by direct calculation and induction. For $k = 0$, we have $q_i(0) = 0$ for $i \geq 2$ by initial condition. Assume the proposition is true for $k$ and corresponding $i$, we have

$$q_{i}^{(k+1)}(0) = \gamma_{i-1} q_{i-1}^{(k)}(0) - (\gamma_i + \mu_i + \sigma_i) q_{i}^{(k)}(0) + \mu_{i+1}q_{i+1}^{(k)}(0) = 0$$

for $i \geq k + 3$ by induction. \qed

**Proposition 4.** $\alpha_{ii} = v_{ii} v_{11} > 0$ for $i = 1, 2, \ldots, N$. 


Proof. Let $\lambda_0 = \max\{|a_{ii}|+1\}$. Then $\lambda_0 I + A$ is a non-negative, irreducible matrix with the same eigenvectors as $A$, and thus $\{v_{i1}\}_{i=1,\ldots,N}$ is a nonzero multiple of the principal eigenvector of the matrix $\lambda_0 I + A$. The fact $v_{i1}v_{i1} > 0$ is a simple corollary of the Perron-Frobenius theorem applied to $\lambda_0 I + A$ (see Theorem 8.4.4 in [9]).

To discuss the oscillatory behavior of $q_i(t)$, we need the following result concerning their behavior as $t \to \infty$.

**Corollary 4.** For $i = 1, 2, \ldots, N$, $k \in \mathbb{N}$, there exists $T_{ik} > 0$ such that $\text{sgn}(q_i^{(k)}(t)) = (-1)^k$ when $t \geq T_{ik}$.

**Proof.** The proof is straightforward by direct calculation and Proposition 4 for the dominant part $\alpha_{i1}e^{\lambda_1 t}$.

**Lemma 3.** Let $i \in \{1, 2, \ldots, N\}$, $k \in \mathbb{N}$. Assume that $q_i^{(k)}(t_j) = 0$ for $j = 1, 2, \ldots, m$, $t_1 < t_2 < \cdots < t_m$. There exist $t_1 < \tilde{t}_1 < t_2 < \cdots < t_m < \tilde{t}_m$ such that $q_i^{(k+1)}(t_j) = 0$, $j = 1, 2, \ldots, m$.

**Proof.** We can find $\tilde{t}_j, 1 \leq j \leq m - 1$, by Rolle’s theorem. To find $\tilde{t}_m$, we prove by contradiction. Otherwise, $q_i^{(k+1)}(t) \neq 0$ for $t \geq t_m$. Applying Corollary 4, we have that for any $t \geq t_m$, $(-1)^{k+1}q_i^{(k+1)}(t) > 0$, moreover

$$\frac{d}{dt}((-1)^k q_i^{(k)}(t)) = (-1)^k q_i^{(k+1)}(t) < 0, \quad t \geq t_m.$$  

Then we get that $(-1)^k q_i^{(k)}(t) < 0$ for any $t \geq t_m$, which is a contradiction with Corollary 4.

Now we are ready to prove the no-oscillation theorem mentioned in the introduction.

**Proof of Theorem 1.** From (14), we only need to prove that $\#\{t : t > 0, q_i(t) = 0\} \leq 1$ for $2 \leq i \leq N$. Argue by contradiction. Otherwise, there exists an $i_0 \geq 2$ such that $\#\{t : t > 0, q_{i_0}(t) = 0\} \geq 2$. Applying Lemma 3, Proposition 3 and Rolle’s theorem on $[0, t_1]$ defined in Lemma 3, we have

$$r(q_{i_0}^{(i_0-1)}) \geq \#\{t : t > 0, q_{i_0}^{(i_0-1)}(t) = 0\} \geq \#\{t : t > 0, q_{i_0}^{(i_0-2)}(t) = 0\} + 1 \geq \cdots \geq \#\{t : t > 0, q_{i_0}^{(i_0-(i_0-1))}(t) = 0\} + i_0 - 2 \geq 2 + i_0 - 2 = i_0.$$  

By Corollary 1 and Lemma 2, we get

$$\text{sc}(q_{i_0}) = \text{sc}(q_{i_0}^{(i_0-1)}) \geq r(q_{i_0}^{(i_0-1)}) \geq i_0,$$

which is a contradiction with Corollary 3.
2.2. Degenerate case. In the degenerate case, \(0 \in \{\gamma_1, \ldots, \gamma_{N-1}, \mu_2, \ldots, \mu_N, \sum_{i=1}^N \sigma_i^2\}\). Denote the system dynamics by

\[
\dot{q} = A_d q, \quad q|_{t=0} = (1, 0, \ldots, 0)^T.
\]

We can find \(\{A_n\}_{n=1}^{\infty}\), where \(A_n\) is non-degenerate and \(\lim_{n \to \infty} \|A_n - A_d\|_\infty = 0\). We also have the no-oscillation theorem by the following monotonically decreasing property of \(q_i\) once it achieves its peak value.

**Theorem 3** (No-oscillation theorem in the degenerate case). For system (18) under Assumption 2, we have that for any \(i, t_1 < t_2 < t_3\), if \(q_i(t_1) > q_i(t_2)\), then \(q_i(t_2) \geq q_i(t_3)\). Moreover, the limit \(\lim_{t \to \infty} q(t)\) exists.

**Proof.** Prove by contradiction. Otherwise, there exists \(i_0, 0 < t_1 < t_2 < t_3 < T\), such that \(q_{i_0}(t_1) > q_{i_0}(t_2) < q_{i_0}(t_3)\). Define \(q^n(t)\) as the solution of

\[
\dot{q}^n = A_n q^n, \quad q^n(0) = (1, 0, \ldots, 0)^T.
\]

Let \(\delta q^n = q^n - q\), we have

\[
\delta \dot{q}^n = A_n q^n - A_d q = (A_n - A_d)q^n, \quad \delta q(0) = 0.
\]

It is a simple observation that \(\|q^n(t)\|_\infty \leq 1\) for any \(t \in \mathbb{R}^+\) by non-negativity of \(q^n\) and the total mass decay/conservation property of the system. We have

\[
\|\delta \dot{q}^n(t)\|_\infty = \left\| \int_0^t e^{A_d(t-s)}(A_n - A_d)q^n(s)ds \right\|_\infty \\
\leq \int_0^t \left\| e^{A_d(t-s)} \right\|_\infty \|A_n - A_d\|_\infty ds \\
\leq T e^{\|A_d\|_\infty T} \|A_n - A_d\|_\infty \to 0 \quad \text{as} \quad n \to \infty.
\]

That is, we obtain \(\lim_{n \to \infty} q^n(t) = q(t)\) for any \(t \in \mathbb{R}^+\). As a result we can choose \(n\) large enough such that

\[
q^n_{i_0}(t_1) > \frac{q_{i_0}(t_1) + q_{i_0}(t_2)}{2}, \\
q^n_{i_0}(t_3) > \frac{q_{i_0}(t_2) + q_{i_0}(t_3)}{2}, \\
q^n_{i_0}(t_2) < \min \left\{ \frac{q_{i_0}(t_1) + q_{i_0}(t_2)}{2}, \frac{q_{i_0}(t_2) + q_{i_0}(t_3)}{2} \right\}.
\]

We get

\[
0 < q^n_{i_0}(t_1) > q^n_{i_0}(t_2) < q^n_{i_0}(t_3).
\]

(19)

Applying Theorem 1, we get contradiction if \(i_0 = 1\) in (19) since \(q^n_{i_0}\) monotonically decreases; if \(i_0 \geq 2\), by the fact \(q_{i_0}(0) = 0\) and Rolle’s Theorem, (19) implies that \(q^n_{i_0}\) has at least two different roots in intervals \((0, t_2)\) and \((t_1, t_3)\), respectively, which is also a contradiction.

The limit \(\lim_{t \to \infty} q(t)\) exists due to the above monotonic property of \(q\) at large \(t\) and the total mass decay/conservation of the system.
3. **Nonlinear system.** In the nonlinear case, we have the equation

\[ \dot{q} = A(q) \cdot 1, \quad q(0) = (1, 0, \ldots, 0)^T, \]

where \(1 = (1, 1, \ldots, 1)^T\) and

\[
A(q) = \begin{pmatrix}
-\gamma_1(q_1) - \sigma_1(q_1) & \mu_2(q_2) & \cdots & 0 \\
\gamma_1(q_1) & -\gamma_2(q_2) - \mu_2(q_2) - \sigma_2(q_2) & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & \mu_N(q_N)
\end{pmatrix}.
\]

Let \(C^\omega(D)\) denote the analytic functions on domain \(D\). First we need some assumptions on the regularity of the system.

**Assumption 3.** For any function \(f \in \{\gamma_1(x), \ldots, \gamma_{N-1}(x), \mu_2(x), \ldots, \mu_N(x), \sigma_1(x), \ldots, \sigma_N(x)\}\), there exists an \(\eta_0 > 0\) such that \(f\) is a real analytic function on \(D = (-\eta_0, \infty)\), i.e. for any \(x_0 \in D\), there exists a neighborhood \(U\) of \(x_0\) such that the Taylor series

\[
f(x) = \sum_{n=0}^{\infty} \frac{f^{(n)}(x_0)}{n!}(x-x_0)^n
\]

converges for \(x \in U\). Such real analytic functions will be denoted by \(C^\omega(D)\) or \(C^\omega\) in later text.

**Assumption 4** (Non-degeneracy and cooperativity). For any function \(f \in \{\gamma_1(x), \ldots, \gamma_{N-1}(x), \mu_2(x), \ldots, \mu_N(x)\}\), we require the conditions

(a) non-degeneracy: \(x = 0, f(x) = 0\) and \(x > 0, f(x) > 0\); \hspace{1cm} (21)

(b) cooperativity: \(x > 0, \dot{f}(x) > 0\). \hspace{1cm} (22)

For \(f \in \{\sigma_1(x), \ldots, \sigma_N(x)\}\), we require that either \(f(x) \equiv 0\), or \(f\) satisfies both conditions (a) and (b). Furthermore, we require

(c) non-degeneracy: \(q \neq 0, \sum_{i=1}^{N} \sigma_i(q_i) > 0\). \hspace{1cm} (23)

In bio-chemical reaction systems, the rate functions usually take the form of polynomials or Hill functions with integer Hill exponents, e.g. \(x^2\) (dimerization) or \(x^n/(1 + x^n)\) (Hill function with exponent \(n\)), thus the above assumptions trivially hold. Note that we take the non-degenerate condition (b) to keep later discussions compact and essential. We will discuss on how to relax condition (c) at the end of this section.

Before jumping into technical details, let us briefly illustrate our proof ideas. First we will show that the critical points of the trajectory are isolated so that we can break the time interval into different units. Within each interval unit the monotonic behavior of any species is kept invariant. We then characterize such monotonic pattern by showing that the concentrations of the first several species always decrease while the concentrations of the other species always increase. The key part of our proof is to demonstrate that the change of the monotonic behavior in neighboring interval units has a domino-like effect. The final proof of Theorem 2 is completed by showing that there exist at most finite such intervals and the last species can only exhibit the single-peak pattern.
The following proposition shows the existence and bounded characteristics of the solution of the nonlinear system (20).

**Proposition 5.** Under Assumptions 3-4, there exists a unique solution $q$ for Cauchy problem (20). Moreover, $0 < q_i(t) < 1$ for any $t > 0$, $i = 1, 2, \ldots, N$.

**Proof.** With the regularity condition on $A(q)$ in Assumption 3, we have the local well-posedness of the initial value problem (20) by the local Lipschitz condition on the right hand side of the system. To get the global well-posedness, we note that the maximum principle holds for the system, i.e. when $q(t) = 0$, we have $q_i(t) \geq 0$ by non-degeneracy condition. This implies that $q_i(t) \geq 0$ for $t \in \mathbb{R}^+$, $i = 1, 2, \ldots, N$.

On the other hand,

$$
\sum_{k=1}^{N} \dot{q}_k(t) = - \sum_{k=1}^{N} \sigma_k(q_k(t)) \leq 0 \quad \text{for } t \geq 0,
$$

we have

$$
\sum_{k=1}^{N} q_k(t) \leq \sum_{k=1}^{N} q_k(0) = 1, \quad t \geq 0,
$$

which means $q_i(t) \leq 1$. The global well-posedness follows by continuation of the local solution.

Next we prove the stronger statement $0 < q_i(t) < 1$ when $t > 0$. Assume $\{t : \exists \epsilon_0 > 0, s.t. q_i(t) = 0\} \neq \emptyset$. We then define $t_0 = \inf \{t : \exists \epsilon_0 > 0, s.t. q_i(t) = 0\} \geq \epsilon_0 > 0$ and assume $q_i(t_0) = 0$. We thus obtain from Assumption 4 and (20)

$$
\dot{q}_i(t_0) = \gamma_{i-1}(q_{i-1}(t_0)) + \mu_{i+1}(q_{i+1}(t_0)) \geq 0 + 0 = 0. \quad (25)
$$

On the other hand, we have

$$
\dot{q}_i(t_0) = \lim_{s \to 0^+} \frac{q_i(t_0 - s) - q_i(t_0)}{-s} \leq 0.
$$

This gives $\dot{q}_i(t_0) = 0$ and $q_i(t_0) = q_i(t_0) = 0$ by (25) and Assumption 4. The induction shows $q(t_0) = 0$.

Define $\tilde{q}(t) = q(t_0 - t)$ for $t \in [0, t_0]$. Then $\tilde{q}(t)$ and $0$ are both solutions of the ODEs $\dot{p} = -A(p) \cdot 1$ on $[0, t_0]$ with initial condition $p(0) = 0$, which contradicts with the uniqueness of the ODE solution. The proof is done. \hfill \Box

Let us recall the following classic theorem concerning the analyticity of the solution of ODEs [17].

**Theorem 4** (ODE Version of Cauchy-Kovalevskaya theorem). Suppose that $a > 0$, $F : (-a, a)^m \to \mathbb{R}^m$, $m \in \mathbb{N}$, is real analytic near $0 \in (-a, a)^m$ and $u(t)$ is the unique solution of the ODEs

$$
\dot{u}(t) = F(u(t)), \quad u(0) = 0.
$$

Then $u$ is also real analytic near $t = 0$.

Here the multi-dimensional real analytic function on $\mathbb{R}^m$ is defined through local convergence of multivariate Taylor series in component-by-component way. It can be easily verified that the right hand side of (20) is real analytic on $D^N$ by Assumption 3 and the separable form of $A(q) \cdot 1$ on each $q_i$.

**Corollary 5.** Under Assumptions 3-4, the solution $q_i \in C^\infty$ for $i = 1, 2, \ldots, N$. 
Define the set of critical points of \( q_i \) by
\[
R_i = \{ t : t \geq 0, \dot{q}_i(t) = 0 \} \quad \text{for } i = 1, 2, \ldots, N
\]
and the set of accumulation points of \( R_i \) by
\[
R'_i = \{ t : t \geq 0, \text{for any } \delta > 0, \exists \text{ infinitely many } t_n \in R_i, \text{s.t. } 0 < |t_n - t| < \delta \}.
\]
It is straightforward to show that \( R'_i \) is closed. Furthermore, we have

**Proposition 6.** \( R'_i = \emptyset \) for \( i = 1, 2, \ldots, N \).

**Proof.** Prove by contradiction. Otherwise, there exists \( i_0 \) such that \( R'_{i_0} \neq \emptyset \). Define \( t_0 = \inf \{ t : t \in R'_{i_0} \} \). We have \( t_0 \in R'_{i_0} \) by the closedness of \( R'_{i_0} \). If \( t_0 > 0 \), we get
\[
q^{(n)}_{i_0}(t_0) = 0 \quad \text{for any } n \geq 1
\]
by \( q_{i_0} \in C^\infty \) and Rolle’s theorem. This implies \( \dot{q}_{i_0}(t) \equiv 0 \) in a neighborhood of \( t_0 \). By the definition of \( t_0 \), we conclude that \( t_0 = 0 \) and
\[
q^{(n)}_{i_0}(0) = 0 \quad \text{for any } n \geq 1. \tag{26}
\]
By Assumption 4, we can show \( q^{(i-1)}_i(0) > 0 \) and \( q^{(k)}_i(0) = 0 \) for \( i = 1, 2, \ldots, N, k \leq i - 2 \) by direct calculation and induction. This contradicts with (26). \( \square \)

To understand the monotonic behavior of \( q \), we define the sets \( S_i \) and \( S_r \) as below.

**Definition 2** (Monotone intervals). Define the sets
\[
S_i = \{ t : q_j(t) < 0 \quad \text{for } j \leq i; \quad \dot{q}_j(t) > 0 \quad \text{for } j > i \}, \quad i = 1, 2, \ldots, N.
\]

**Definition 3** (Set of critical points). Define the set of roots of all \( q_i \)
\[
S_r = \{ t : t \geq 0, \quad \dot{q}_i(t) = 0 \quad \text{for some } i \}.
\]

According to Proposition 6, \( S_r \) can be listed in ascending order as \( S_r = \{ a_i \}_{i=0}^{N_r} \). We have \( a_0 = 0 \) and
\[
a_j < a_{j+1}, \quad 0 \leq l < N_r.
\]
We then have the decomposition \([0, \infty) \setminus S_r = \bigcup_{i=0}^{N_r} (a_i, a_{i+1})\), where \( a_{N_r+1} := \infty \). It is obvious that \( \dot{q}_i(t) \neq 0 \) for any \( i \) and \( t \in (a_i, a_{i+1}) \). Later we will show \( N_r < \infty \). But so far let us assume that \( N_r = \infty \) is possible. For simplicity in later text, we will use an abused notation \((a_l, a_{l+1}) \in \{ S_1, S_2, \ldots, S_{N_r} \} \) to indicate that \((a_l, a_{l+1}) \subset S_k \) for some \( k \in \{i_1, i_2, \ldots, i_m\} \).

From Proposition 7 to 11, we always assume that the index \( l \), appearing in \((a_{l-1}, a_l)\), is a finite integer in \( \{1, 2, \ldots, N_r\} \).

**Proposition 7.** Assume \((a_{l-1}, a_l) \subset S_i\). Denote \( d_j = \min \{ k : k \in \mathbb{N}, k \geq 1, q^{(k)}_j(a_l) \neq 0 \} \). We have
\[
\text{sgn}(q^{(d_j)}_j(a_l)) = \text{sgn}((-1)^{d_j}) \quad \text{for } j \leq i,
\]
\[
\text{sgn}(q^{(d_j)}_j(a_l)) = -\text{sgn}((-1)^{d_j}) \quad \text{for } j > i.
\]
Correspondingly for any \( 1 \leq m \leq d_j \), we have
\[
(-1)^m q^{(m)}_j(a_l) \geq 0 \quad \text{for } j \leq i,
\]
\[
(-1)^m q^{(m)}_j(a_l) \leq 0 \quad \text{for } j > i. \tag{27}
\]
Proof. According to the proof in Proposition 6, we have $d_j < \infty$, otherwise $q_j(t) \equiv q_j(a_l)$ in a neighbourhood of $a_l$, which is a contradiction according to the definition of $S_i$ and $(a_{l-1}, a_l) \subset S_i$. For sufficiently small $\epsilon > 0$, the sign of $\dot{q}_j(t)$ in $(a_l - \epsilon, a_l)$ is decided by the sign of the $(d_j - 1)$-th term of the Taylor expansion of $\dot{q}_j(t)$

$$
\frac{\dot{q}_j^{(d_j)}(a_l)}{(d_j - 1)!} (-1)^{d_j - 1} \left\{ \begin{array}{ll}
< 0, & j \leq i, \\
> 0, & j > i,
\end{array} \right.
$$

which exactly gives the desired result. \hfill \square

Our key observation on $q$ is the domino-like monotonic pattern proven in Propositions 8-12.

**Proposition 8.** $(a_0, a_1) \subset S_1$.

**Proof.** First we have $\dot{q}_1(0) < 0$, $\dot{q}_2(0) > 0$, and $\dot{q}_j(0) = 0$ for $j \geq 3$ by (20). We claim that $\dot{q}_j(t) > 0$ on $(a_0, a_1)$ for $j \geq 3$. Otherwise, there exists $j_0 \geq 3$ such that $\dot{q}_{j_0}(t) < 0$ on $(a_0, a_1)$. We have

$$
\dot{q}_{j_0}(t) = \int_0^t \dot{q}_{j_0}(s) ds < 0 \quad \text{for } t < a_1,
$$

which is a contradiction with Proposition 5. \hfill \square

**Proposition 9.** Assume $(a_{l-1}, a_l) \subset S_1$. Then $\dot{q}_1(a_l) < 0$ and $(a_l, a_{l+1}) \subset S_1$ or $S_2$.

**Proof.** First we have $\dot{q}_1(a_l) \leq 0$ and $\dot{q}_k(a_l) \geq 0$ for $k \geq 2$ by condition $(a_{l-1}, a_l) \subset S_1$. According to the definition of $S_i$, there exists $j_0$ such that $\dot{q}_{j_0}(a_l) = 0$. We will prove the proposition by discussing different possibilities of $j_0$.

**Case I.** $j_0 = 1$. By Proposition 5, we have

$$
0 \leq \dot{q}_1(a_l) + \sum_{k=2}^N \dot{q}_k(a_l) = - \sum_{k=1}^N \sigma_k(q_k(a_l)) < 0,
$$

which is a contradiction. This also implies that $\dot{q}_1(a_l) < 0$.

**Case II.** $j_0 > 2$. By (27) in Proposition 7, we get

$$
0 \geq \dot{q}_{j_0}(a_l) \\
= \dot{\gamma}_{j_0-1}(q_{j_0-1}(a_l))q_{j_0-1}(a_l) + \mu_{j_0+1}(q_{j_0+1}(a_l))q_{j_0+1}(a_l) \\
\geq 0 + 0 = 0,
$$

(28)

where the last term will disappear if $j_0 = N$. We get $\dot{q}_{j_0+1}(a_l) = 0$ and $\dot{q}_{j_0}(a_l) = 0$ from (28). By induction, we obtain $\dot{q}_k(a_l) = 0$, $k \geq 2$; $\dot{q}_k(a_l) = 0$, $k \geq 3$. Applying Proposition 7 again, we get

$$
0 \leq q_3^{(3)}(a_l) = \dot{\gamma}_2(q_2(a_l))q_2^{(2)}(a_l) = \dot{\gamma}_2(q_2(a_l))\dot{\gamma}_1(q_1(a_l))\dot{q}_1(a_l) < 0,
$$

which is a contradiction. So Case II can be excluded.

**Case III.** $j_0 = 2$. This is the only admissible case.

In this case, we have $\dot{q}_2(a_l) = 0$ and $\dot{q}_k(a_l) \neq 0$ for any $k \neq 2$. This means that $\dot{q}_k(t)$ can not change sign through $a_l$ for $k \neq 2$. So there exists $\epsilon > 0$, such that for any $t \in (a_l, a_l + \epsilon)$,

$$
\dot{q}_k(t) < 0, \quad k = 1,
\dot{q}_k(t) > 0, \quad k > 2.
$$

Then $(a_l, a_{l+1}) \subset S_1$ or $S_2$. \hfill \square
Proposition 10. If \((a_{l-1}, a_l) \subset S_N\), then \(l = N_r + 1\) and \(N_r < \infty\).

Proof. Prove by contradiction. Otherwise, we have \(N_r = \infty\), \(l < \infty\) or \(N_r < \infty\) and \(l \leq N_r\). In both cases, \(a_l < \infty\) and there exists \(j_0\) such that \(\dot{q}_{j_0}(a_l) = 0\). By Proposition 7 and the condition \((a_{l-1}, a_l) \subset S_N\), we get

\[
0 \leq \dot{q}_{j_0}(a_l) = \gamma_{j_0-1}(q_{j_0-1}(a_l))\dot{q}_{j_0-1}(a_l) + \mu_{j_0+1}(q_{j_0+1}(a_l))\dot{q}_{j_0+1}(a_l) \leq 0 + 0 = 0,
\]

where the last term will disappear if \(j_0 = N\). Thus we obtain \(\dot{q}_k(a_l) = 0\) for \(k = 1, 2, \ldots, N\) by induction, which contradicts with

\[
\sum_{k=1}^{N} \dot{q}_k(a_l) = \sum_{k=1}^{N} \sigma_k(q_k(a_l)) < 0. \tag{29}
\]

The proof is done. \(\square\)

Proposition 11. For \(2 \leq i \leq N - 1\) and \(1 \leq l \leq N_r\) \((N_r < \infty)\) or \(l \geq 1\) \((N_r = \infty)\), if \((a_{l-1}, a_l) \subset S_i\), then \((a_i, a_{i+1}) \in \{S_{i-1}, S_i, S_{i+1}\}\).

Proof. First we have \(\dot{q}_k(a_l) \leq 0\) for \(k \leq i\) and \(\dot{q}_k(a_l) \geq 0\) for \(k > i\) by condition \((a_{l-1}, a_l) \subset S_i\). There exists \(j_0\) such that \(\dot{q}_{j_0}(a_l) = 0\). We discuss different possibilities of \(j_0\).

Case I. \(j_0 < i\). With similar approach in proving Proposition 10, we will get \(\dot{q}_k(a_l) = 0\) for \(k \leq i\) by induction and \(\dot{q}_k(a_l) \geq 0\) for \(k > i\) by the condition \((a_{l-1}, a_l) \subset S_i\), which contradicts with (29).

As Case I is excluded, we have

\[
\dot{q}_k(a_l) < 0 \quad \text{for } k < i. \tag{30}
\]

Case II. \(j_0 = i\) and \(\dot{q}_{i+1}(a_l) = 0\). By Proposition 7 and (30), we have

\[
0 \leq \dot{q}_i(a_l) = \dot{q}_{i-1}(q_{i-1}(a_l))\dot{q}_{i-1}(a_l) + \mu_{i+1}(q_{i+1}(a_l))\dot{q}_{i+1}(a_l) < 0,
\]

which is a contradiction.

Case III. \(j_0 > i + 1\). With similar approach in Case II of Proposition 9, we will get \(\dot{q}_k(a_l) = 0\), \(k > i\); \(\dot{q}_k(a_l) = 0\), \(k > i + 1\). Thus

\[
0 \leq \dot{q}_{i+2}(a_l) = \dot{q}_{i+1}(q_{i+1}(a_l))\dot{q}_{i+1}(a_l) = \dot{q}_{i}(q_{i}(a_l))\dot{q}_{i}(a_l). \tag{31}
\]

If \(\dot{q}_i(a_l) < 0\), we get contradiction with (31); otherwise \(\dot{q}_i(a_l) = 0\), which also gives contradiction from the same inequalities used in Case II since \(\dot{q}_i(a_l) \geq 0\).

There are only two cases left and now we have

\[
\dot{q}_k(a_l) < 0 \quad \text{for } k < i,
\]

\[
\dot{q}_k(a_l) > 0 \quad \text{for } k > i + 1.
\]

Case IV. \(\dot{q}_i(a_l) = 0\), \(\dot{q}_{i+1}(a_l) > 0\). Then there exists \(\epsilon > 0\) such that for \(t \in (a_i, a_{i+1} + \epsilon)\), we obtain

\[
\dot{q}_k(t) < 0 \quad \text{for } k < i,
\]

\[
\dot{q}_k(t) > 0 \quad \text{for } k > i + 1.
\]
We get \((a_l, a_{l+1}) \subset S_{l-1}\) or \(S_l\).

**Case V.** \(\dot{q}_i(a_l) < 0, \dot{q}_{i+1}(a_l) = 0\). Then there exists \(\epsilon > 0\) such that for \(t \in (a_l, a_l + \epsilon)\), we obtain
\[
\dot{q}_k(t) < 0 \quad \text{for } k < i + 1.
\]
\[
\dot{q}_k(t) > 0 \quad \text{for } k > i + 1.
\]
We get \((a_l, a_{l+1}) \subset S_l\) or \(S_{l+1}\). Notice that in this case, if \(i = N - 1\), then \((a_l, a_{l+1}) \subset S_N\) and \(a_{l+1} = \infty\) since we have \(\dot{q}_N(t) < 0\) in \((a_l, a_{l+1})\) by
\[
\dot{q}_N(a_l) = \gamma_{N-1}(q_{N-1}(a_l))\dot{q}_{N-1}(a_l) < 0
\]
and Proposition 10.

Summarize the above discussions, we get the result. \(\square\)

**Lemma 4.** For \(l = 0, 1, \ldots, N_r\), we have \((a_l, a_{l+1}) \in \{S_1, S_2, \ldots, S_N\}\).

**Proof.** Combining the results of Propositions 8-11, we have
\[
(a_l, a_{l+1}) \in \{S_1, S_2, \ldots, S_N\}
\]
for \(0 \leq l \leq N_r\) \((N_r < \infty)\) or \(0 \leq l < \infty\) \((N_r = \infty)\). \(\square\)

**Proposition 12.** \(N_r < \infty\).

**Proof.** Prove by contradiction. Otherwise, we have \((a_l, a_{l+1}) \in \{S_1, S_2, \ldots, S_{N-1}\}\) by Proposition 10 and Lemma 4. Then \(\dot{q}_N(t) \geq 0\) for \(t \in \mathbb{R}^+\). So \(q_N(t) \geq q_N(1) > 0\) for \(t \geq 1\). Let us denote \(q_N(1) = b_N\).

**Case I.** If \(\sigma_N(x) \neq 0\), we have
\[
\sum_{i=1}^{N} (q_i(t) - q_i(1)) = \int_1^t \sum_{i=1}^{N} \dot{q}_i(s)ds = -\int_1^t \sum_{i=1}^{N} \sigma_i(q_i(s))ds
\]
\[
\leq -\int_1^t \sigma_N(q_N(s))ds
\]
\[
\leq -(t-1)\sigma_N(b_N) \rightarrow -\infty \quad \text{as } t \rightarrow \infty,
\]
which contradicts with
\[
\sum_{i=1}^{N} (q_i(t) - q_i(1)) \geq -1.
\]

**Case II.** \(\sigma_N(x) \equiv 0, \sigma_{N-1}(x) \neq 0\). As \(\dot{q}_N(t) \geq 0\), we have
\[
\gamma_{N-1}(q_{N-1}(t)) \geq \mu_N(q_N(t)) \geq \mu_N(q_N(1)), \quad t \geq 1,
\]
which means
\[
q_{N-1}(t) \geq \gamma_{N-1}^{-1}(\mu_N(q_N(1))) > 0, \quad t \geq 1.
\]
Denote \(b_{N-1} = \gamma_{N-1}^{-1}(\mu_N(q_N(1)))\). With similar procedure in Case I, we get the contradiction since
\[
\sum_{i=1}^{N} (q_i(t) - q_i(1)) = \int_1^t \sum_{i=1}^{N} \dot{q}_i(s)ds = -\int_1^t \sum_{i=1}^{N} \sigma_i(q_i(s))ds
\]
\[
\leq -\int_1^t \sigma_{N-1}(q_{N-1}(s))ds
\]
\[
\leq -(t-1)\sigma_{N-1}(b_{N-1}) \rightarrow -\infty \quad \text{as } t \rightarrow \infty.
\]
Case III. $\sigma_N(x), \sigma_{N-1}(x) \equiv 0, \sigma_{N-2}(x) \neq 0$. We have

$$\dot{q}_{N-2}(t) \geq \mu_{N-1}(b_{N-1}) - \gamma_{N-2}(q_{N-2}(t)) - \mu_{N-2}(q_{N-2}(t)) - \sigma_{N-2}(q_{N-2}(t)).$$

Denote the solution of the equation

$$\mu_{N-1}(b_{N-1}) - \gamma_{N-2}(x) - \mu_{N-2}(x) - \sigma_{N-2}(x) = 0, \quad x \in (0, 1)$$

by $s_{N-2}$. If the solution does not exist, we have $\dot{q}_{N-2}(t) \geq 0$ for $t \in \mathbb{R}^+$, and similar arguments in Case I gives the contradiction. Otherwise let us define

$$b_{N-2} = \min\{s_{N-2}, q_{N-2}(1)\} > 0.$$

If there exists $t_0 > 1$ such that $q_{N-2}(t_0) < b_{N-2},$ we can define

$$t_1 = \sup\{t \in [1, t_0] : q_{N-2}(t) \geq b_{N-2}\}. \quad (32)$$

Then according to the definition, $q_{N-2}(t) < b_{N-2} \leq s_{N-2}$ for $t_1 < t < t_0$. So $\dot{q}_{N-2}(t) > 0$ for $t_1 < t < t_0$ by the monotonicity of $\gamma_{N-2}, \mu_{N-2}$ and $\sigma_{N-2},$ which contradicts with $q_{N-2}(t_0) < b_{N-2} = q_{N-2}(t_1)$ by the definition (32). So we have $q_{N-2}(t) \geq b_{N-2}$ for $t \geq 1.$ With similar procedure in Case I, we get the contradiction since

$$\sum_{i=1}^{N}(q_i(t) - q_i(1)) = \int_1^t \sum_{i=1}^{N}\dot{q}_i(s)ds = -\int_1^t \sum_{i=1}^{N}\sigma_i(q_i(s))ds$$

$$\leq -\int_1^t \sigma_{N-2}(q_{N-2}(s))ds$$

$$\leq -(t-1)\sigma_{N-2}(b_{N-2}) \to -\infty \quad \text{as} \quad t \to \infty.$$

Case IV. $\sigma_N(x), \sigma_{N-1}(x), \sigma_{N-2}(x) \equiv 0, \sigma_{N-3}(x) \neq 0$. Similar argument as the Case III for $q_{N-3}(t)$ will lead to the contradiction.

This procedure can be repeated with respect to $q_{N-4}$ and so on. We will finally stop at some $q_k$ since we assume that at least one $\sigma_k(x) \neq 0$ in Assumption 5. Then we get the contradiction. \hfill \Box

Proof of Theorem 2. Applying Lemma 4 and Propositions 8-12 together, we have

$$\dot{q}_1(t) < 0 \quad \text{for} \quad t > 0,$$

$$\dot{q}_N(t) > 0 \quad \text{for} \quad 0 < t < a_N,$$

$$\dot{q}_N(t) < 0 \quad \text{for} \quad t > a_N,$$

which means $\#\{t : t > 0, \dot{q}_1(t) = 0\} = 0$ and $\#\{t : t > 0, \dot{q}_N(t) = 0\} = 1.$

Because $\dot{q}_i(t) < 0$ for $i = 1, 2, \ldots, N$ on $(a_N, \infty)$, we get that $\lim_{t \to \infty} q_i(t)$ exists, which is denoted by $q_i(\infty)$. Substitute into (20), we obtain

$$\sum_{i=1}^{N}\sigma_i(q_i(\infty)) = 0,$$

which gives $q(\infty) = 0$ by condition (c) in Assumption 4. \hfill \Box

In general, for the species which does not correspond to $q_1$ or $q_N$, i.e. the first or last one, respectively the signal might have oscillations, which is different from the linear case. Two simple three-node systems with quadratic or Hill function type reaction rates are given below as illustrative counter-examples.
Example 2.

\[
\begin{pmatrix}
\dot{q}_1 \\
\dot{q}_2 \\
\dot{q}_3
\end{pmatrix} =
\begin{pmatrix}
-0.3q_1^2 & 0.6q_2 & 0 \\
0.3q_1^2 & -2.4q_2 & q_3^2 \\
0 & 1.8q_2 & -q_3^2 - 0.01q_3
\end{pmatrix}
\begin{pmatrix}
1 \\
1 \\
1
\end{pmatrix},
q(0) = e_1.
\]

The solution curve for \(q_2(t)\) with oscillations is shown in Fig. 2. This example perfectly illustrates the conceptual difference between our no-oscillation theorem and the deficiency zero theorem. It can be easily verified that the deficiency of this reaction network is zero. So there is no positive cyclic composition trajectory by the deficiency zero theorem. However, we say that the species \(q_2\) has oscillations in the sense that it is not of a single peak pattern, which is clearly observed from Figure 2.

Example 3.

\[
\begin{align*}
\dot{q}_1 &= -1.5q_1^2 + 0.2q_2^2, \\
\dot{q}_2 &= 1.5q_1^2 - 2.2q_2^2 + 1.3q_3^2, \\
\dot{q}_3 &= 2.0q_2^2 - 1.3q_3^2 - 0.01q_3,
\end{align*}
\]

\(q(0) = e_1\).

The solution curve for \(q_2(t)\) with oscillations is shown in Fig. 3.

**Figure 2.** The oscillations can appear for the middle species when the system is nonlinear. Shown here is the solution of \(q_2\) for a three-node example with quadratic reaction rates.

**Remark 1.** The condition (c) in Assumption 4 can be relaxed to \(\sigma_i(x) \equiv 0\) for any \(i\), i.e. the total mass is conservative. With this condition, we will have that \(q_N\) monotonically increases to a positive equilibrium state. That is, the statement of the main theorem should be modified as

\[
\dot{q}_1(t) < 0, \quad \dot{q}_N(t) > 0 \text{ for } t > 0, \quad \lim_{t \to \infty} q(t) = q(\infty).
\]
The proof is almost the same by trivial modifications. Three key points should be paid attention. First, we will only have \( N - 1 \) classes \( \{ S_1, S_2, \ldots, S_{N-1} \} \) for the intervals \( (a_{i-1}, a_i) \). And when \( (a_{i-1}, a_i) \subset S_{N-1} \), we touch the end of the domino bricks, i.e. \( l = N_r + 1 \) and \( N_r = \infty \). This is different from the non-degenerate case. Second, in the places where we use the decay property \( -\sum_{k=1}^{N} \sigma_k(q_k(a_j)) < 0 \), the inequality sign \( '<' \) is replace with \( '=' \). Then we get \( \dot{q}(t) = 0 \) at some finite \( t > 0 \). The contradiction here turns to be that the equilibrium state can not be reached in a finite time since otherwise it would violate the uniqueness of ODE solution. Third, in the place where we prove Case V in Proposition 11, we need to notice that the case \( i = N - 1 \) and \( \dot{q}_N(t) = 0 \) must be excluded since it breaks the total mass conservation.

4. Generalization to branching-structured network. After finishing the discussion on the no-oscillation theorem in linear signal transduction pathway, let us consider more complex transduction pathways with branching structure (Figure 4). We first study a system with one main backbone, denoted by \( S^m_k \) \((k = 1, \ldots, N_m)\), and two sub-branches, denoted by \( S^l_k \) \((k = 1, \ldots, N_l)\) and \( S^r_k \) \((k = 1, \ldots, N_r)\), respectively.

When the considered system dynamics in Fig. 4 is linear, we have the governing equation

\[
\dot{q} = Aq, \quad q(0) = e_1.
\]  

(33)

Here the dimension of \( q \) is \( N = N_m + N_l + N_r \) with components

\[
q = (q^m, q^l, q^r),
\]
where \( q^m, q^l \) and \( q^r \) correspond to the block \( S^m_k, S^l_k \) and \( S^r_k \), respectively. The structure of \( A \) has the form

\[
A = \begin{pmatrix}
A_m & 0 & 0 & 0 & 0 & 0 \\
\vdots & \ddots & 0 & \vdots & \ddots & 0 \\
\mu^*_l & \cdots & 0 & \mu^*_l & \cdots & 0 \\
0 & \cdots & \gamma^*_l & 0 & \cdots & 0 \\
0 & \cdots & 0 & \gamma^*_l & \cdots & 0 \\
0 & \cdots & 0 & 0 & A_l & 0 \\
0 & \cdots & 0 & 0 & 0 & A_r \\
0 & \cdots & 0 & 0 & 0 & 0
\end{pmatrix},
\]

(34)

where \( A_m, A_l \) and \( A_r \) have similar structure as considered in Sect. 2 and the non-degenerate type conditions are assumed about the rates.

**Assumption 5.** The matrices \( A_m, A_l \) and \( A_r \) have the same structure as \( A \) considered in Eq. 3, and they all satisfy Assumption 1. Moreover, we also assume \( \gamma^*_l, \gamma^*_r, \mu^*_l, \mu^*_r > 0 \).

According to Proposition 1, there exists diagonal matrices \( D_m, D_l, D_r \) such that

\[
A'_m = D_m^{-1} A_m, A'_l = D_l^{-1} A_l D_l, A'_r = D_r^{-1} A_r D_r
\]

are symmetric matrices. Without loss of generality, we take the components

\[
D_m(N_m, N_m) = D_l(1, 1) = D_r(1, 1) = 1
\]

and define

\[
B = \left( \begin{array}{ccc}
D_m & 0 & 0 \\
0 & \sqrt{\frac{\gamma^*_l}{\mu^*_l}} D_l & 0 \\
0 & 0 & \sqrt{\frac{\gamma^*_r}{\mu^*_r}} D_r
\end{array} \right)^{-1} A \left( \begin{array}{ccc}
D_m & 0 & 0 \\
0 & \sqrt{\frac{\gamma^*_l}{\mu^*_l}} D_l & 0 \\
0 & 0 & \sqrt{\frac{\gamma^*_r}{\mu^*_r}} D_r
\end{array} \right).
\]
Then we have

\[
B = \begin{bmatrix}
A'_m & 0 & 0 & 0 \\
\vdots & \ddots & \ddots & \vdots \\
\sqrt{\gamma^*_l \mu^*_l} & \cdots & 0 & \sqrt{\gamma^*_r \mu^*_r} \\
0 & \cdots & \sqrt{\gamma^*_r \mu^*_r} & \cdots & 0 \\
0 & \ddots & \vdots & 0 & \cdots & \vdots \\
0 & 0 & \ddots & \vdots & 0 & \cdots & \vdots \\
0 & 0 & 0 & \cdots & 0 & \ddots & \vdots \\
& & & & & & 0 & \cdots & \sqrt{\gamma^*_l \mu^*_l} \\
& & & & & & 0 & \cdots & \sqrt{\gamma^*_r \mu^*_r} \\
\end{bmatrix},
\]

which is symmetric. In this branching case, the result like Proposition 2 does not hold, but as \(A\) is similar to the symmetric matrix \(B\), it has \(N\) linearly independent eigenvectors. So similar equation like (12) still holds except that the eigenvalues may not be distinct. However, with similar procedure in proving Theorem 1, we can still obtain the following theorem.

**Theorem 5.** For system (33) with Assumption 5, we have \(\lim_{t \to \infty} q(t) = 0\), \(q_1(t) < 0\) for \(t \in \mathbb{R}^+\) and \(#\{t : t > 0, \dot{q}_i(t) = 0\} \leq 1\) for \(2 \leq i \leq N_m\).

The proof is almost the same as the linear chain case except a slight difference since the eigenvalues may not be distinct. We have to collect the terms corresponding to same eigenvalues together in (12). This induces to a corresponding change in the proof of Corollary 3. We have to consider the index \(i\) varying from 2 to \(N_m\) instead of \(N\), and change the terms \(v^2_{ij}\) to \(\sum_{j \in J} v^2_{ij}\), where \(v_j\) corresponds to a same eigenvalue if \(j \in J\). The equality in the last line of Eq. (17) should be replaced by ‘\(\leq\’ since \(\sum_{j \in J} v^2_{ij}\) may be 0, but the conclusion is not affected. So in the following discussion, we assume that the eigenvalues are distinct for simplicity.

We can also show that the signal does not have oscillations for the ending species in each branch. Similarly, we have the following proposition corresponding to Corollary 3.

**Proposition 13.** For system (33) with Assumption 5, \(i_0 = N_m + N_l\), \(sc(q_{i_0}) \leq i_0 - 1\).

**Proof.** Note that we have

\[
q_{i_0}(t) = \sum_{j=1}^{N} \alpha_{i_0j} e^{\lambda_j t}, \quad \alpha_{i_0j} = v_{i_0j} v_{1j}
\]

by the distinct eigenvalues assumption mentioned above.

Let \(A'_m\) denote the \(i \times i\) upper-left submatrix of \(A_m\). By Lemma 1, we have

\[
\frac{v_{N_mj}}{v_{1j}} = \frac{\det(\lambda_j I - A_{N_m-1}^m)}{\prod_{k=2}^{N} \mu_k^m}, \quad j = 1, \ldots, N.
\]

Let \(A'_l\) denote the \(i \times i\) bottom-right submatrix of \(A_l\). With similar approach in Lemma 1 but from the last to the first row of \(A_l\), we obtain

\[
\frac{v_{N_mj}}{v_{i_0j}} = \frac{\det(\lambda_j I - A_{N_l}^l)}{\gamma_l^* \prod_{k=1}^{N_l} \gamma_k^{-1}}, \quad j = 1, \ldots, N.
\]
Thus we get
\[
\frac{v_{i_0j}}{v_{1j}} = \frac{\det(\lambda_j I - A_m^{-1}) \gamma_i \prod_{k=1}^{N_l-1} \gamma_k^j}{\det(\lambda_j I - A_l) \prod_{k=2}^{N_l-1} \mu_k^m} = \frac{\det(\lambda_j I - A_m^{-1}) \det(\lambda_j I - A_l) \gamma_i \prod_{k=1}^{N_l-1} \gamma_k^j}{(\det(\lambda_j I - A_l))^2 \prod_{k=2}^{N_l} \mu_k^m}.
\]

The difficulty of the discussion about the sign change of \(q_i\) lies on the singularity of the term \(1/\det(\lambda_j I - A_l)^2\). So we define a new function \(p(\lambda)\) as below
\[
p(\lambda) = \begin{cases} 
\det(\lambda I - A_m^{-1}) \det(\lambda I - A_l), & \det(\lambda I - A_l) \neq 0, \\
\alpha_{i_0j}, & \lambda = \lambda_j \text{ and } \det(\lambda_j I - A_l) = 0.
\end{cases}
\]

Applying similar techniques in Corollary 3, we have
\[
\text{sc}(q_{i_0}) = \text{sc}(\alpha_{i_01}, \alpha_{i_02}, \ldots, \alpha_{i_0N}) \leq \text{sc}(p(\lambda_1), p(\lambda_2), \ldots, p(\lambda_N)).
\]

Note that the root or discontinuity point of \(p(\lambda)\) must be the root of \(\det(\lambda I - A_m^{-1}) \det(\lambda_j I - A_l)\). Similar as Corollary 3, let us discuss the sign change variation when such a root is passed.

**Case I.** \(\lambda\) is a root with odd multiplicity of \(\det(\lambda I - A_m^{-1}) \det(\lambda_j I - A_l)\). The sign of \(p(\lambda)\) in the neighborhood of \(\lambda\) must be one ‘+’ and one ‘−’ in this case. The sign change is 1 in this case no matter what sign \(\alpha_{i_0j}\) is. So in this case, the number of roots will be added by \(2k - 1\) (\(k \geq 1\)) and the sign change variation will be 1. The conclusion is not affected.

**Case II.** \(\lambda\) is a root with even multiplicity of \(\det(\lambda I - A_m^{-1}) \det(\lambda_j I - A_l)\). The sign of \(p(\lambda)\) in two sides can be the same this case, so the sign change will be 0/2 if they have same/opposite sign with \(\alpha_{i_0j}\). So in this case, the number of roots will be added by \(2k\) (\(k \geq 1\)) and the sign change variation will be 0/2. The conclusion is not affected, either.

Overall we conclude that
\[
\text{sc}(p(\lambda_1), p(\lambda_2), \ldots, p(\lambda_N)) \leq r(\det(\lambda I - A_m^{-1}) \det(\lambda I - A_l)) = i_0 - 1.
\]

The proof is done. \(\square\)

Note that the case of \(i = N_m + N_l + N_r\) follows by the symmetry of \(N_l\) and \(N_r\).

As a consequence, we have

**Theorem 6.** For system (33) with Assumption 5, \(\# \{t : t > 0, \dot{q}_i(t) = 0\} \leq 1\) for \(i \in \{N_m + N_l, N_m + N_l + N_r\}\).

The two theorems presented above indicate that the no-oscillation theorem still holds for the main backbone and two last nodes in the two sub-branches of the linear transduction pathway. However, the signal might have oscillations for the other species in the sub-chains. We present an explicit example to demonstrate this point (Figure 5).

For more complicate tree-structured network, it may have more sub-chains in a single level or have more levels (Figure 6). Below we will briefly discuss about the oscillation structure studied previously. The proof can be given by mimicking the steps in Sections 2 and 3 and Theorems 5-6 with minor modifications in a straightforward way.
For the tree network topology which has only two levels but with more than two sub-branches, we can prove that the solutions for the species in the main backbone and the ending species in the sub-branches do not involve oscillations.

For the tree network topology which has more than two levels, we can prove that the solutions for the species in the main backbone do not involve oscillations, while the oscillations may appear for all other species in the sub-branches. In Example 4, we present an explicit example to show this fact.

For nonlinear case, we can only prove that the solution for the starting species does not involve oscillation, while the oscillations may appear for the other species. In Example 5, we present an explicit example to show this fact.

Example 4. In this example, we will show that the oscillations may appear for all species in the sub-branches if there are more than two levels in the tree-structured linear transduction pathway.

For simplicity, we consider the network topology shown in the right panel of Fig. 6. We make the following correspondence between the species in different...
levels and the subscript indices of $q$:

$$(S_0, S_1^1, S_1^2, S_2^1, S_2^2, S_3^1) \rightarrow (1, 2, 3, 4, 5, 6, 7).$$

Below we will only present the chosen matrix $A$ and the specific solution curve involving oscillations for a selected species.

- In Figure 7, $q_2$, the species $S_1^1$ in the 2nd level, involves oscillations.
- In Figure 8, $q_4$, the species $S_2^1$ in the 3rd level, involves oscillations.

$$\begin{pmatrix}
-1.7 & 0.2 & 1.6 & 0 & 0 & 0 & 0 \\
0.3 & -5 & 0 & 1 & 0.7 & 0 & 0 \\
1.3 & 0 & -2.6 & 0 & 0 & 1.1 & 0.3 \\
0 & 1.5 & 0 & -1.1 & 0 & 0 & 0 \\
0 & 3.2 & 0 & 0 & -0.8 & 0 & 0 \\
0 & 0 & 0.8 & 0 & 0 & -1.2 & 0 \\
0 & 0 & 0.1 & 0 & 0 & 0 & -0.4 \\
\end{pmatrix}$$

**Figure 7.** Left panel: matrix $A$. Right panel: oscillatory behavior of $q_2$. The inset figure shows the amplified detail of $q_2$.

$$\begin{pmatrix}
-1.01 & 0.40 & 0.30 & 0 & 0 & 0 & 0 \\
0.10 & -3.31 & 0 & 2.40 & 0.10 & 0 & 0 \\
0.90 & 0 & -0.71 & 0 & 0 & 1.20 & 0.70 \\
0 & 1.20 & 0 & -2.41 & 0 & 0 & 0 \\
0 & 1.70 & 0 & 0 & -0.11 & 0 & 0 \\
0 & 0 & 0.20 & 0 & 0 & -1.21 & 0 \\
0 & 0 & 0.20 & 0 & 0 & 0 & -0.71 \\
\end{pmatrix}$$

**Figure 8.** Left panel: matrix $A$. Right panel: oscillatory behavior of $q_4$.

**Example 5.** Consider the nonlinear system

$$\begin{pmatrix}
\dot{q}_1 \\
\dot{q}_2 \\
\dot{q}_3 \\
\dot{q}_4 \\
\end{pmatrix} =
\begin{pmatrix}
-1.5q_1^2 & 1.2q_2 & 0 & 0 \\
1.5q_1^2 & -2.1q_2 & 1.4q_3^2 & 2.2q_4^2 \\
0 & 0.7q_2 & -1.4q_3^2 & 0 \\
0 & 0.2q_2 & 0 & -2.2q_4^2 - 0.01q_4 \\
\end{pmatrix}\begin{pmatrix}
1 \\
1 \\
1 \\
1 \\
\end{pmatrix}, \quad q(0) = e_1,$$

which corresponds to the network topology in Figure 9. $q_4$ involves oscillations although it corresponds to the ending species in a sub-branch.

**5. Conclusion.** The considered system in this paper covers a class of biochemical reaction networks describing intracellular signal transduction pathways. For such kind of systems, a stimulation such as growth factor act as a starting signal. The signal then propagate along the transduction network. With damping mechanism, the signal will finally vanish after a sufficiently long time. Except this limiting
behavior characterization, we focus on the oscillatory pattern of the magnitude of signal for each species.

For a simple non-degenerate linear signal transduction system, we show that the magnitude of signal of the starting species decreases monotonically. Moreover, for the other nodes, a single peak pattern is proved to be the only possibility. For a more general nonlinear signal transduction system where nonlinear reactions such as Michaelis-Menten kinetics is included, we prove the monotonic behavior of the starting species and single peak pattern of the ending species. For middle species, we present an explicit example to show that the oscillation is possible. This means that if we neglect complex behavior in the middle reaction processes, a signal from upstream will only cause a single peak signal downstream. Similar results are also generalized to the systems without damping or with branching structures. A complete landscape for the no-oscillation property of linear signal transduction pathway is established.

So, mathematically, we prove that the dynamical oscillation is impossible for networks with certain topology. This will be useful in understanding the general connection between the biological dynamics and network topologies, which will also provide insights on the choice of mathematical models when dealing with biological data. According to our theorem, the feedback or delay mechanism is generally necessary to create oscillations even for a simple chain or tree-like network.

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