**Supplementary Information:** PENDISC: A Simple Method for Constructing a Mathematical Model from Time-Series Data of Metabolite Concentrations

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Supplementary Information 1: Additional information

1.1 Simple case study for linear metabolic pathway model with inhibition

Let us consider the following S-system equations that are derived from the linear network shown in Fig. S1.

\[
\begin{align*}
\frac{dX_1}{dt} &= 12X_3^{-0.8} - 10X_1^{0.5} \\
\frac{dX_2}{dt} &= 10X_1^{0.5} - 3X_2^{0.75} \\
\frac{dX_3}{dt} &= 3X_2^{0.75} - 5X_3^{0.5}
\end{align*}
\]

(S1)

The initial values for the metabolite concentrations are chosen as \(X_{10} = 1.4, X_{20} = 2.7\), and \(X_{30} = 1.2\). The steady-state metabolite concentrations are as follows; \(X_1^* = 0.4902\), \(X_2^* = 3.0958\), and \(X_3^* = 1.9610\). In an actual system, these concentrations must be determined from measured values. Firstly, values of 0.5 or –0.5 are assigned to the kinetic orders in Eq. (S1) to obtain the following equations.

\[
\begin{align*}
\frac{dX_1}{dt} &= \alpha_1X_3^{-0.5} - \beta_1X_1^{0.5} \\
\frac{dX_2}{dt} &= \beta_1X_1^{0.5} - \beta_2X_2^{0.5} \\
\frac{dX_3}{dt} &= \beta_2X_2^{0.5} - \beta_3X_3^{0.5}
\end{align*}
\]

(S2)

Secondly, Eq. (S2) is non-dimensionalized using steady-state concentrations, followed by applying the constraints:

\[
\begin{align*}
A_2 &= (X_1^* / X_2^*)A_1 \\
A_3 &= (X_1^* / X_3^*)A_1
\end{align*}
\]

(S3)

which mathematical operation leads to
\[ \frac{dx_1}{dt} = A_1(x_3^{-0.5} - x_1^{0.5}) \]
\[ \frac{dx_2}{dt} = A_2(x_1^{0.5} - x_2^{0.5}) = A_1 \frac{X_1^*}{X_2^*} (x_1^{0.5} - x_2^{0.5}) \]
\[ \frac{dx_3}{dt} = A_3(x_2^{0.5} - x_3^{0.5}) = A_1 \frac{X_1^*}{X_3^*} (x_2^{0.5} - x_3^{0.5}) \]

(S4)

where

\[ A_1 = \alpha X_3^{-0.5}, \quad A_2 = \beta X_1^{0.5} = \beta_2 X_2^{0.5}, \quad A_3 = \beta_2 X_2^{0.5} = \beta_3 X_3^{0.5}. \]  

(S5)

Lastly, the value of \( A_1 \) is determined by a nonlinear least-squares method so as to fit the solution to Eq. (S4) to the time-series data.

In general, the chance of the parameter estimation converging increases as the number of unknown parameters decreases. Fortunately, the PENDISC method can markedly reduce the number of unknown parameters using the constraints derived from the structure of the network. To confirm the validity of this operation, the parameter estimation in the linear metabolic pathway model with inhibition (Fig. S1) was performed for two cases, one in which the values of \( A_1, A_2, \) and \( A_3 \) are unknown, and a second in which only the value of \( A_1 \) is unknown. Figure S2 shows a comparison of the results obtained using the estimated rate constants with the time-series data of metabolite concentrations; the left vertical axis shows the actual metabolite concentration, and the right vertical axis shows the dimensionless metabolite concentration. It should be noted that these two metabolite concentrations are different in magnitude, but vary in the same manner. Eleven concentration data points were used for each metabolite, and the initial values of \( A_i \) were all set to 5. The rate constants determined for different numbers of unknown parameters are listed in Table S1 (Supplementary Information 2). The agreement between the calculated results and the time-series data is reasonable, but not perfect. This is because the kinetic orders in the S-system equations were set to 0.5 or \(-0.5\). In every case, the calculated lines successfully exhibit time-transient behaviors analogous to the time-series data. The agreement is higher in the case of three unknown rate constants than in the case of one unknown rate constant. This is because the former case has more flexibility for changing the shape of the calculated line, as there are more adjustable parameters. However, it should be noted that when three dimensionless rate constants are unknown, the relevant equations do not satisfy the constraints. In theory, the calculated result can satisfy the
constraints only when $A_1$ is unknown and other dimensionless rate constants are expressed as a function of $A_1$. The calculation time was 6.34 s for the case of three unknown parameters, and this shortened to 4.67 s for the case of one unknown parameter.

Evidently, a reduction in the number of unknown parameters is the major advantage of the PENDISC method. When the pathway is linear, all the relevant differential equations are expressed in terms of the dimensionless rate constant of the first metabolite ($A_1$), regardless of the total number of metabolites. If the steady-state values and time-series data are available for all metabolites, the rate constants $\alpha_i$ and $\beta_i$ ($i = 1, 2, \ldots, n$) can be obtained by simply determining $A_1$ in order to fit the calculated values to the time-series data for all metabolite concentrations.

1.2 Equations for branched pathway model with inhibition and activation

Let us consider the following S-system equations derived from the network structure with a branched pathway shown in Fig. 2 in the manuscript (Voit and Almeida, 2004).

\[
\begin{align*}
\frac{dX_1}{dt} &= 12X_3^{-0.8} - 10X_1^{0.5} \\
\frac{dX_2}{dt} &= 8X_1^{0.5} - 3X_2^{0.75} \\
\frac{dX_3}{dt} &= 3X_2^{0.75} - 5X_3^{0.5}X_4^{0.2} \\
\frac{dX_4}{dt} &= 2X_1^{0.5} - 6X_4^{0.8} 
\end{align*}
\]

(S6)

The initial values for the metabolite concentrations are chosen as

\[X_{10} = 1.4, X_{20} = 2.7, X_{30} = 1.2, \text{ and } X_{40} = 0.4.\] (S7)

The steady-state concentrations are as follows; $X_1^* = 0.3996, X_2^* = 2.0061, X_3^* = 2.2284,$ and $X_4^* = 0.1428$. Firstly, values of 0.5 or –0.5 are assigned to the kinetic orders in Eq. (S6) to obtain the following equations.
\[
\frac{dX_1}{dt} = \alpha_1 X_1^{-0.5} - \beta_1 X_1^{0.5}
\]
\[
\frac{dX_2}{dt} = \alpha_2 X_2^{0.5} - \beta_2 X_2^{0.5}
\]
\[
\frac{dX_3}{dt} = \beta_2 X_2^{0.5} - \beta_3 X_3^{0.5} X_4^{0.5}
\]
\[
\frac{dX_4}{dt} = \alpha_4 X_4^{0.5} - \beta_4 X_4^{0.5}
\]

(S8)

Secondly, Eq. (S8) is non-dimensionalized using steady-state concentrations, followed by applying the constraints:

\[
A_2 = (X_1^* A_1 - X_4^* A_4) / X_2^*, \quad A_3 = (X_1^* A_1 - X_4^* A_4) / X_3^*.
\]

(S9)

which leads to

\[
\frac{dx_1}{dt} = A_1(x_1^{0.5} - x_1^{0.5})
\]
\[
\frac{dx_2}{dt} = A_2(x_2^{0.5} - x_2^{0.5}) = \frac{A_1 X_1^* - A_4 X_4^*}{X_2^*}(x_1^{0.5} - x_2^{0.5})
\]
\[
\frac{dx_3}{dt} = A_3(x_3^{0.5} - x_3^{0.5} x_4^{0.5}) = \frac{A_1 X_1^* - A_4 X_4^*}{X_3^*}(x_2^{0.5} - x_3^{0.5} x_4^{0.5})
\]
\[
\frac{dx_4}{dt} = A_4(x_4^{0.5} - x_4^{0.5})
\]

(S10)

with the following dimensionless rate constants.

\[
A_1 = \alpha_1 X_1^{0.5} / X_1^*, \quad A_2 = \alpha_2 X_1^{0.5} / X_2^*, \quad A_3 = \beta_2 X_2^{0.5} / X_2^*, \quad A_4 = \alpha_4 X_4^{0.5} / X_4^*
\]

(S11)

Lastly, two unknown parameters included in Eq. (S10), \(A_1\) and \(A_4\), are determined by a nonlinear least-squares method so as to fit the solution to Eq. (S10) to the time-series data.

1.3 Equations for aspartate-derived amino acid biosynthesis model

The aspartate-derived amino acid biosynthesis in plants is controlled by several feedback inhibitions and activations and forms a relatively complicated network
structure shown in Fig. 3 in the manuscript. The mathematical model for this system consists of seven differential equations with the flux expressions in Michaelis-Menten form (Curien, et al., 2009). The kinetic parameters in the expressions have been determined by in vitro measurement of metabolite concentrations in the plant model, Arabidopsis. In the following, we investigated the performance of the PENDISC method by regarding the time-series data in in silico calculation as experimental data.

When the mathematical model is transformed into S-system equations and a value of 0.5 or –0.5 is assigned to the kinetic orders, the following equations are obtained.

\[
\begin{align*}
\frac{dX_1}{dt} &= \alpha_1 X_3^{-0.5} X_6^{-0.5} - \beta_1 X_1^{0.5} \\
\frac{dX_2}{dt} &= \beta_1 X_1^{0.5} - \beta_2 X_2^{0.5} X_3^{-0.5} X_6^{-0.5} \\
\frac{dX_3}{dt} &= \alpha_2 X_2^{0.5} X_3^{-0.5} - \beta_3 X_3^{0.5} \\
\frac{dX_4}{dt} &= \alpha_4 X_3^{0.5} X_6^{-0.5} - \beta_4 X_4^{0.5} \\
\frac{dX_5}{dt} &= \beta_4 X_4^{0.5} - \beta_5 X_5^{0.5} \\
\frac{dX_6}{dt} &= \beta_5 X_5^{0.5} - \beta_6 X_6^{0.5} X_7^{-0.5} \\
\frac{dX_7}{dt} &= \beta_6 X_6^{0.5} X_7^{-0.5} - \beta_7 X_7^{0.5}
\end{align*}
\]

(S12)

The initial values for the metabolite concentrations are chosen as

\[
\begin{align*}
X_{10} &= 0.688, & X_{20} &= 0.9645, & X_{30} &= 69.3809, & X_{40} &= 0.9368, \\
X_{50} &= 45.2733, & X_{60} &= 302.3907, & X_{70} &= 59.2472
\end{align*}
\]

(S13)

The model provides the steady-state concentrations as follows; \(X_1^* = 0.3440\), \(X_2^* = 0.9645\), \(X_3^* = 69.3809\), \(X_4^* = 0.9368\), \(X_5^* = 45.2733\), \(X_6^* = 302.3907\), and \(X_7^* = 59.2472\).

Eq. (S12) is routinely non-dimensionalized using these values, followed by applying the constraints:

\[
\begin{align*}
A_2 &= (X_1^* / X_2^*) A_4, & A_3 &= (X_3^* A_4 - X_4^* A_2) / X_3^* = (X_1^* A_4 - X_4^* A_2) / X_3^* \\
A_5 &= (X_4^* / X_5^*) A_4, & A_6 &= (X_5^* / X_6^*) A_4, & A_7 &= (X_4^* / X_7^*) A_4
\end{align*}
\]

(S14)

which leads to
\[
\frac{dx_1}{dt} = A_1 \left( x_3^{-0.5} x_6^{-0.5} - x_1^{0.5} \right)
\]
\[
\frac{dx_2}{dt} = A_2 \left( x_1^{0.5} - x_2^{0.5} x_3^{-0.5} x_6^{-0.5} \right) = A_1 \frac{X_1^*}{X_2^*} \left( x_1^{0.5} - x_2^{0.5} x_3^{-0.5} x_6^{-0.5} \right)
\]
\[
\frac{dx_3}{dt} = A_4 \left( x_2^{0.5} x_3 x_5^{0.5} - x_3^{0.5} \right) = \frac{X_1^* A_1 - X_4^* A_4}{X_3^*} \left( x_2^{0.5} x_3 x_5^{0.5} - x_3^{0.5} \right)
\]
\[
\frac{dx_4}{dt} = A_4 \left( x_2^{0.5} x_6 - x_4^{0.5} \right)
\]
\[
\frac{dx_5}{dt} = A_5 \left( x_4^{0.5} - x_5^{0.5} \right) = A_4 \frac{X_4^*}{X_5^*} \left( x_4^{0.5} - x_5^{0.5} \right)
\]
\[
\frac{dx_6}{dt} = A_6 \left( x_5^{0.5} - x_6^{0.5} x_7^{-0.5} \right) = A_4 \frac{X_5^*}{X_6^*} \left( x_5^{0.5} - x_6^{0.5} x_7^{-0.5} \right)
\]
\[
\frac{dx_7}{dt} = A_7 \left( x_6^{0.5} x_7 - x_7^{0.5} \right) = A_4 \frac{X_6^*}{X_7^*} \left( x_6^{0.5} x_7 - x_7^{0.5} \right)
\]

with the following dimensionless rate constants.

\[
A_1 = \alpha_1 X_3^{-0.5} X_6^{-0.5} / X_1^* = \beta_1 X_1^{0.5} / X_1^*,
\]
\[
A_2 = \beta_2 X_1^{0.5} / X_2^* = \beta_2 X_2^{0.5} X_3^{-0.5} X_6^{-0.5} / X_2^*,
\]
\[
A_3 = \alpha_3 X_2^{0.5} X_3^{-0.5} / X_3^* = \beta_3 X_3^{0.5} / X_3^*,
\]
\[
A_4 = \alpha_4 X_2^{0.5} X_6^{-0.5} / X_4^* = \beta_4 X_4^{0.5} / X_4^*,
\]
\[
A_5 = \beta_5 X_4^{0.5} / X_5^* = \beta_5 X_5^{0.5} / X_5^*,
\]
\[
A_6 = \beta_6 X_5^{0.5} / X_6^* = \beta_6 X_6^{0.5} X_7^{-0.5} / X_6^*,
\]
\[
A_7 = \beta_7 X_6^{0.5} X_7^{-0.5} / X_7^* = \beta_7 X_7^{0.5} / X_7^*
\]

Eq. (S15) includes two unknown parameters, \( A_1 \) and \( A_4 \). This is because the present network model possesses one branching point (\( p=1 \)) and therefore, the number of parameters becomes equal to 2 by \( 1+p \). Lastly, \( A_1 \) and \( A_4 \) are determined by a nonlinear least-squares method so as to fit the solution to Eq. (S15) to the time-series data.
Supplementary Information 2: Additional tables

**Table S1** Parameters estimated in a linear metabolic pathway model with inhibition

| Parameters | Number of unknown parameters |
|------------|------------------------------|
|            | 3                            |
|            | 1                            |
| $A_1$      | 10.91306                     |
| $A_2$      | 2.56352                      |
| $A_3$      | 5.29521                      |
| $\alpha_1$| 7.49190                      |
| $\alpha_2$| 11.33469                     |
| $\alpha_3$| 5.90152                      |
| $\beta_1$ | 7.64102                      |
| $\beta_2$ | 4.51051                      |
| $\beta_3$ | 7.41511                      |

**Table S2** Mean square error (MSE) from leave-one-out cross validation in a branched pathway model with inhibition and activation

| Cases                                | Mean Square Errors (MSE)  |
|--------------------------------------|---------------------------|
| Original data                        | 4.257729394011472e-03     |
| Original data without P1 (leave data at t=0.5 out) | 5.292934493602961e-03     |
| Original data without P2 (leave data at t=1.0 out) | 5.049823299379336e-03     |
| Original data without P3 (leave data at t=1.5 out) | 4.192754658754883e-03     |
| Original data without P4 (leave data at t=2.0 out) | 4.171368192927286e-03     |
| Original data without P5 (leave data at t=2.5 out) | 4.239005265752483e-03     |
| Original data without P6 (leave data at t=3.0 out) | 4.263600386371204e-03     |
| Original data without P7 (leave data at t=3.5 out) | 4.251004518991907e-03     |
| Original data without P8 (leave data at t=4.0 out) | 4.251371094692189e-03     |
| Original data without P9 (leave data at t=4.5 out) | 4.256641447206231e-03     |
| Original data without P10 (leave data at t=5.0 out) | 4.257691739470663e-03     |
Table S3  Dimensionless rate constants estimated under different conditions in a branched pathway model with inhibition and activation

|                  | Number of data points |
|------------------|-----------------------|
|                  | 11        | 21        | 51        |
| 4A15-A1          | 37.40380  | 21.30459  | 20.14537  |
| 4A15-A2          | 4.43753   | 5.12628   | 5.19780   |
| 4A15-A3          | 5.82703   | 4.20929   | 3.96235   |
| 4A15-A4          | 23.65609  | 136.04615 | 5019.22171|
| 4A I10-A1        | 37.40380  | 21.30459  | 20.14534  |
| 4A I10-A2        | 4.43753   | 5.12628   | 5.19825   |
| 4A I10-A3        | 5.82703   | 4.20929   | 3.96243   |
| 4A I10-A4        | 23.65609  | 136.04614 | 5019.20585|
| 3A I5-A1         | 28.92633  | 22.04351  | 20.45549  |
| 3A I5-A2         | 5.12280   | 4.92922   | 4.73220   |
| 3A I5-A3         | 4.61176   | 4.43749   | 4.26013   |
| 3A I5-A4         | 36.46860  | 95.18853  | 4938.25547|
| 3A I10-A1        | 28.92633  | 22.04351  | 20.46039  |
| 3A I10-A2        | 5.12280   | 4.92922   | 4.73178   |
| 3A I10-A3        | 4.61176   | 4.43749   | 4.25974   |
| 3A I10-A4        | 36.46860  | 95.18853  | 4938.42454|
| 2A I5-A1         | 36.12924  | 35.72481  | 35.25168  |
| 2A I5-A2         | 4.96854   | 4.74889   | 4.71687   |
| 2A I5-A3         | 4.47289   | 4.27515   | 4.24633   |
| 2A I5-A4         | 31.30257  | 33.25723  | 32.38298  |
| 2A I10-A1        | 36.12924  | 35.72481  | 35.25168  |
| 2A I10-A2        | 4.96854   | 4.74889   | 4.71687   |
| 2A I10-A3        | 4.47289   | 4.27515   | 4.24633   |
| 2A I10-A4        | 31.30257  | 33.25723  | 32.38297  |

*) The numerical values before the character "A" and after the character "I" indicate the number of unknown parameters and the value used as the initial guesses, respectively.
Table S4 $\chi^2$, calculation times, and iterations with different conditions in a branched pathway model with inhibition and activation

| Conditions          | Number of data points | 11   | 21   | 51   |
|---------------------|-----------------------|------|------|------|
| 4A Initial5 $\rightarrow$ $\chi^2$ |                      | 0.05898 | 0.30021 | 0.93860 |
| Calculation time (s) |                      | 9.51  | 813.06 | 35874.42 |
| Iteration (times)   |                      | 16    | 733   | 4854  |
| 4A Initial10 $\rightarrow$ $\chi^2$ |                      | 0.05898 | 0.30021 | 0.93860 |
| Calculation time (s) |                      | 9.86  | 55.15 | 34994.06 |
| Iteration (times)   |                      | 19    | 35    | 4780  |
| 3A Initial5 $\rightarrow$ $\chi^2$ |                      | 0.06925 | 0.30321 | 0.97750 |
| Calculation time (s) |                      | 9.53  | 34.06 | 66353.40 |
| Iteration (times)   |                      | 21    | 16    | 8768  |
| 3A Initial10 $\rightarrow$ $\chi^2$ |                      | 0.06925 | 0.30321 | 0.97750 |
| Calculation time (s) |                      | 7.12  | 31.82 | 64585.90 |
| Iteration (times)   |                      | 13    | 17    | 9074  |
| 2A Initial5 $\rightarrow$ $\chi^2$ |                      | 0.07441 | 0.43083 | 1.56563 |
| Calculation time (s) |                      | 15.48 | 69.55 | 556.67 |
| Iteration (times)   |                      | 37    | 45    | 50    |
| 2A Initial10 $\rightarrow$ $\chi^2$ |                      | 0.07441 | 0.43083 | 1.56563 |
| Calculation time (s) |                      | 13.51 | 66.35 | 555.75 |
| Iteration (times)   |                      | 30    | 41    | 49    |

*) The numerical value before the character “A” indicates the number of unknown parameters and that after the word “Initial” represents the value used as the initial guesses.
**Table S5** Rate constants estimated in a branched pathway model with inhibition and activation in a case of unmeasurable $X_2$.

| $X_i$ | $\alpha_i$ | $\beta_i$ |
|-------|------------|------------|
| $X_1$ | 23.63709   | 25.05008   |
| $X_2$ | 19.66911   | 7.38125    |
| $X_3$ | 7.38125    | 22.04390   |
| $X_4$ | 5.38097    | 9.00239    |

**Table S6** Parameters estimated in an aspartate-derived amino acid biosynthesis model.

| $X_i$ | $A_i$     | $\alpha_i$ | $\beta_i$ |
|-------|-----------|------------|------------|
| $X_1$ | 6.44094   | 320.96584  | 3.77791    |
| $X_2$ | 2.29758   | 3.77791    | 326.82616  |
| $X_3$ | 0.01045   | 6.15125    | 0.08707    |
| $X_4$ | 1.59116   | 26.39523   | 1.54010    |
| $X_5$ | 0.03293   | 1.54010    | 0.22155    |
| $X_6$ | 0.00493   | 0.22155    | 0.65983    |
| $X_7$ | 0.02516   | 0.65983    | 0.19366    |
Supplementary Information 3: Additional figures

Fig. S1  Linear metabolic pathway model with inhibition
Fig S2  Comparisons of the calculated lines based on three estimated parameters (3A–solid lines) and one parameter (1A–broken lines) with 11 time-series data for each metabolite in a linear metabolic pathway model with inhibition. The left vertical axis shows the actual metabolite concentration, whereas the right vertical axis shows the dimensionless metabolite concentration.
Fig. S3 Count numbers of values of kinetic orders for several models: (1) Amino acid biosynthetic network (Stephanopoulos and Simpson, 1997), (2) Methionine cycle (Reed, et al., 2004), (3) Modified TCA cycle (Shiraishi and Savageau, 1992), (4) Purin metabolism (Curto, et al., 1998)
Fig. S4 Comparisons of the calculated lines based on 2 estimated parameters for kinetic orders of 0.25 or −0.25 (black lines), kinetic orders of 0.50 or −0.50 (red lines), kinetic orders of 0.75 or −0.75 (blue lines), kinetic orders of 1.0 or −1.0 (green lines) with 11 time-series data for each metabolite in a branched pathway model with inhibition and activation
Fig. S5 Comparisons of the calculated lines based on 2 estimated parameters while one point of the time-series data taken from 11 time-series data for all metabolites were removed one-by-one (from data point 1 to 10 with calculated lines P1 to P10, respectively) in a branched pathway model with inhibition and activation.
Fig. S6 Predictions of metabolic behaviors after perturbing $X_1$ (red), $X_2$ (green), $X_3$ (blue) and $X_4$ (black), respectively, two-folds at $t=0$ using the model constructed by PENDISC (simulation lines) compared with \textit{in silico} 11 time-series data generated by the model with actual parameter values for both rate constants and kinetic orders.
Fig. S7 Comparisons of calculated lines based on two, three, and four estimated parameters (represented by the symbols “2A,” “3A,” and “4A,” respectively) with 11, 21 and 51 time-series data for each metabolite in a branched metabolic pathway model with inhibition and activation. The left, middle, and right columns represent the results for different numbers of time-series data. The initial guesses were all set to either 5 or 10 (represented by the symbols “initial 5” and “initial 10,” respectively).
Fig. S8 Comparisons of calculated lines based on estimated 2 parameters with 11 time-series data for each metabolite except $X_2$ in a branched pathway model with inhibition and activation using different initial values of $X_2$ ($x_{20}$ for case 1=2.7/2.006073, $x_{20}$ for case 2=1.0 and $x_{20}$ for case 3=2.0, respectively). Solid lines indicate actual concentrations whereas broken lines indicate normalized concentrations.
Fig. S9 Comparisons of calculated lines based on 2 estimated parameters with 21 time-series data for each metabolite in an aspartate-derived amino acid biosynthesis model. The initial guesses were all set to be 5.
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