Consider a simple metabolic network consisting of three reactions involving four metabolites A, B, C and E:

\[
\begin{align*}
C & \xrightarrow{v_1} A + B \\
2E & \xrightarrow{v_2} B + C \\
O & \xrightarrow{v_3} E,
\end{align*}
\]

where \(O\) denotes the environment.

For this reaction network the stoichiometric matrix is given by:

\[
S = \begin{pmatrix}
1 & 0 & 0 \\
1 & 1 & 0 \\
-1 & 1 & 0 \\
0 & -2 & 1
\end{pmatrix},
\]

where rows correspond to metabolites and columns to reactions, respectively.

Thus, the differential equations of the network are given by:

\[
\begin{align*}
\frac{dA}{dt} &= v_1, \\
\frac{dB}{dt} &= v_1 + v_2, \\
\frac{dC}{dt} &= -v_1 + v_2, \\
\frac{dE}{dt} &= -2v_2 + v_3,
\end{align*}
\]

which represent changes in metabolite levels in terms of the reaction rates \(v_m\), \(1 \leq m \leq 3\).
A general optimization problem including a dynamic model described by differential equations can be posed as:

Objective : \[ \text{max } f(t) \quad t \in [t_0, t_f] \]
\[ s.t. \]
\[ \frac{du}{dt} = F[u(t), z(t), t] \]
\[ u(t_0) = u_0 \]
\[ u(t)^L \leq u(t) \leq u(t)^U \]
\[ z(t)^L \leq z(t) \leq z(t)^U, \]

where \( f(t) \) is an objective function, \( u(t) \) denotes the state profile vector, and \( z(t) \) is a control profile vector, while \( u_0 \) give the initial conditions for the state profile vector. The bounds of the state profile vector are \( u(t)^L, u(t)^U \) and the bounds of the control profile vector are \( z(t)^L, z(t)^U \).

A linear optimization problem that includes the differential equations for the four metabolites A, B, C and E is then given by:

Objective : \[ \text{max } f(t) \quad t \in [t_0 = 0, t_f = 3] \]
\[ s.t. \]
\[ \frac{dA}{dt} = v_1 \]
\[ \frac{dB}{dt} = v_1 + v_2 \]
\[ \frac{dC}{dt} = -v_1 + v_2 \]
\[ \frac{dE}{dt} = -2v_2 + v_3 \]
\[ A(t_0) = A_0 = 2 \]
\[ B(t_0) = B_0 = 2 \]
\[ C(t_0) = C_0 = 2 \]
\[ E(t_0) = E_0 = 2 \]
\[ 0 = A(t)^L \leq A(t) \leq A(t)^U = 100 \]
\[ 0 = B(t)^L \leq B(t) \leq B(t)^U = 100 \]
\[ 0 = C(t)^L \leq C(t) \leq C(t)^U = 100 \]
\[ 0 = E(t)^L \leq E(t) \leq E(t)^U = 100 \]
\[ 0 = v_m(t)^L \leq v_m(t) \leq v_m(t)^U = 100 \quad m = 1, \ldots, 3, \]

where \( v_m \) are the flux rates of the reactions. In case of the simple metabolic network, \( v_m(t) \) are the components of the control profile vectors and \( A(t), B(t), C(t) \) and \( E(t) \) are the components of the state profile vectors. Moreover, as an objective function, the maximization the sum over the concentration of metabolite E at different time points \( (f(t) = \sum E(t)) \) can be used.
**Collocation method**

An optimization problem including differential equations cannot be solved directly. Before solving the problem a solution for the differential equations needs to be determined. Therefore, the differential equations can be solved by different approximation techniques. In our case, we use the orthogonal collocation method to approximate the exact solution for the system of ordinary differential equations (ODEs) [1]. Suppose we have a differential equation, with a differential operator D acting on a function u:

$$D(u(t)) = \frac{du}{dt}, \quad t \in [t_0, t_f],$$

with \( u(t_0) = u_0 \). Hence, the differential equation of metabolite A can be described by:

$$D(A(t)) = \frac{dA}{dt}, \quad t \in [t_0, t_f],$$

with \( A(t_0) = A_0 \), where \( A_0 \) represents the initial concentration of metabolite A at time point \( t_0 \). In general we are interested in the function \( u \), which we want to approximate by \( \tilde{u} \), where \( \tilde{u} \) is a combination of polynomials:

$$u(t) \cong \tilde{u}(t) = \sum_{j=0}^{K} a_j \cdot \phi_j(t).$$

As polynomials, one most commonly uses the family of Lagrange polynomials whereby

$$\phi_j(t) = \prod_{\substack{0 \leq k \leq K \\kappa \neq j}} \frac{t - t_k}{t_j - t_k}.$$  

In the majority of cases, the polynomial given in Eq. (5) can only be used for the state profile vectors due to missing initial conditions for the control profile vectors \( z(t) \). Thus, the approximation by polynomials for \( z(t) \) is defined as follows:

$$z(t) \cong \tilde{z}(t) = \sum_{j=1}^{K} b_j \cdot \psi_j(t); \quad \psi_j(t) = \prod_{\substack{1 \leq k \leq K \\kappa \neq j}} \frac{t - t_k}{t_j - t_k}.$$  

The result of the differentiation of \( \tilde{u}(t) \) is not, in general \( \frac{du}{dt} \). This yields to a residual equation [2]:

$$R(t) = \frac{d\tilde{u}(t)}{dt} - \frac{du(t)}{dt}.$$  

For our example the residual equation of metabolite A is given by:

$$R_A(t) = \frac{d\tilde{A}(t)}{dt} - \frac{dA(t)}{dt},$$

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where $\hat{A}(t)$ is the description of the unknown exact solution for $A(t)$ by the assumed polynomials. The aim of collocation methods is to force the results of $R(t)$ to zero. Then, the discretization of the residual equation based on the method of collocation is performed as follows:

$$\int_{t_0}^{t_f} R(t) \delta(t - t_i) dt = 0, \quad i = 1, \ldots, K,$$

(10)

where $\delta$ represents the Dirac delta function [3] and $t_0$ and $t_f$ are the bounds of the interval (time period). The Dirac delta function has the property that it is zero everywhere except at the origin, where it is infinite:

$$\delta(x) = \begin{cases} +\infty, & \text{if } x = 0 \\ 0, & \text{if } x \neq 0. \end{cases}$$

(11)

A schematic representation of the function is given in Figure 1. The Dirac delta function is not a true function, formally it can be defined as a distribution. At $x_0 = 0$ the distribution is infinity, consequently the result is a finite integral:

$$\int_{-\infty}^{\infty} \delta(x) dx = 1.$$

(12)

For an integrable function $f(x)$ we have that

$$\int_{-\infty}^{\infty} f(x) \delta(x) dx = f(0),$$

(13)

which states that the integral of any function multiplied by the Dirac delta function is just the value of the function at zero. If the Dirac Delta function is shifted to $x = x_0$ by definition of $\delta(x - x_0)$ the result is just the value of the function $f$ at $x_0$:

$$\int_{-\infty}^{\infty} f(x) \delta(x - x_0) dx = f(x_0).$$

(14)
Accordingly, the integral over the residual function $R(t)$ can be written as:

\[
R(t_i) = \frac{d\hat{u}(t_i)}{dt} - \frac{du(t_i)}{dt} = \sum_{j=0}^{K} a_j \cdot \frac{d\phi_j(t_i)}{dt} - \frac{du(t_i)}{dt}, \quad i = 1, \ldots, K, \quad (15)
\]

where $t_i$ are discrete points.

The evaluation of the polynomials at discrete points $t_i$, $t_0 < t_i < t_f$, reduces to the coefficients $a_j$ at these points due to the Lagrange condition, defined by $u_j(t_i) = \delta_{ji}$, where in this case $\delta_{ji}$ is the Kronecker delta. The Kronecker delta is a function of two variables, defined as follows:

\[
\delta_{ji} = \begin{cases} 
1, & \text{if } j = i \\
0, & \text{if } j \neq i.
\end{cases} \quad (16)
\]

Therefore, only a solution for the unknown coefficients $a_j$ needs to be found. The location of the points $t_i$, $i = 1, \ldots, K$, named collocation points, are chosen to correspond to the shifted roots of an orthogonal Legendre polynomial of degree $K$ [1]. Note that Legendre polynomials are solutions to the Legendre’s differential equation:

\[
\frac{d}{dx} \left[ (1 - x^2) \frac{d}{dx} P_n(x) \right] + n(n + 1)P_n(x) = 0. \quad (17)
\]

For example the fifth order Legendre polynomial is defined by:

\[
P_5(x) = \frac{1}{8} (63x^5 - 70x^3 + 15x), \quad (18)
\]

which obviously results in five (orthogonal) roots. For a time period of $t_0 = 0$ and $t_f = 1$ the roots are shown in Figure 2.

\[
\text{Figure 2: Orthogonal roots of the fifth order Legendre polynomial in the interval } [t_0 = 0, t_f = 1], \text{ where } t_1 = 0.0469101, \quad t_2 = 0.23076535, \quad t_3 = 0.5, \quad t_4 = 0.76923465 \text{ and } t_5 = 0.9530899.
\]

Parameterizing the dynamic equations of the metabolites A, B, C and E results in the representation of the seven variables (for metabolite concentrations and flux rates) by novel parameters at each orthogonal root, depicted in Figure 3.
Therefore, the equations for metabolite $A$ considering $K = 5$ at the orthogonal roots are given by:

$$A(t_i) = A_0 \cdot \phi_0(t_i) + A_1 \cdot \phi_1(t_i) + A_2 \cdot \phi_2(t_i) + A_3 \cdot \phi_3(t_i) + A_4 \cdot \phi_4(t_i) + A_5 \cdot \phi_5(t_i), \quad i = 1, \ldots, 5. \quad (19)$$

Hence, the equation $\frac{dA}{dt} = v_1$ is parameterized at the roots of the orthogonal polynomial by the following:

$$A_0 \cdot \phi_0(t_i) + A_1 \cdot \phi_1(t_i) + A_2 \cdot \phi_2(t_i) + A_3 \cdot \phi_3(t_i) + A_4 \cdot \phi_4(t_i) + A_5 \cdot \phi_5(t_i) - (v_1_i) = 0, \quad i = 1, \ldots, 5, \quad (20)$$

with

$$\dot{\phi}_j(t_i) = \frac{d\phi_j}{dt}, \quad j = 0, \ldots, 5. \quad (21)$$

The equations of the metabolites $B$, $C$ and $E$ can be parameterized analogously.

**Extension to orthogonal collocation on finite elements**

Above we describe the global collocation. The global collocation requires a very large number of coefficients for an acceptable approximation of functions that contain both steep fronts and flat regions (requiring a very large $K$). An alternative to global collocation uses piecewise polynomial approximations. For the extension from the global (orthogonal) collocation to orthogonal collocation on finite elements, the interval (time period) is divided into a number of intervals, named *finite elements* [4, 5, 6]. Orthogonal collocation is then applied to each finite element. A finite element $\Delta \zeta_n$ with $n = 1, \ldots, e$, where $e$ is the number of finite elements, is bounded by two points $\zeta_n$ and $\zeta_{n+1}$ with $\Delta \zeta_n = \zeta_n - \zeta_{n+1}$. The
orthogonal properties obtained with global collocation are preserved by mapping the interval \( t \in [t_0, t_f] \) used in the global collocation into each finite element \( \Delta \zeta_n \) by \( \zeta_n = t_0 \) and \( \zeta_{n+1} = t_f \). Thus, the location of the Legendre polynomials are mapped to the points:

\[
t_{n,i} = \zeta_n + t_i, \quad n = 1, \ldots, e \quad i = 0, \ldots, K. \tag{22}
\]

In Figure 4, \( K = 5 \) and the number of finite elements is three (\( e = 3 \)). Accordingly, the orthogonal roots of \( \Delta \zeta_2 \) from the example in Figure 4 are given by \( t_{2,1} = 1.0469101, t_{2,2} = 1.23076535, t_{2,3} = 1.5, t_{2,4} = 1.76923465 \) and \( t_{2,5} = 1.9530899 \).

Figure 4: Illustration of the evaluation points in an example with \( K = 5 \) and \( e = 3 \). Considered are the time period \([t_0 = 0, t_f = 3]\).

With help of the orthogonal collocation on finite elements the solution of the differential equations can now be approximated by:

\[
\tilde{u}(t) = \sum_{j=0}^{K} a_{n,j} \cdot \phi_j(t); \quad \phi_j(t) = \prod_{0 \leq k \leq K \atop k \neq j}^{} \frac{t - t_{n,k}}{t_{n,j} - t_{n,k}}, \quad n = 1, \ldots, e. \tag{23}
\]

To enforce continuity at the endpoints of each finite element the polynomial \( \tilde{u}(t) \) is extrapolated to \( t_{n,f} \) with

\[
\tilde{u}(\zeta_{n+1}) = \tilde{u}(t_{n,f}) = \sum_{j=0}^{K} a_{n,j} \cdot \phi_j(t_{n+1,0}) = \sum_{j=0}^{K} a_{n,j} \cdot \phi_j(t_{n,f}), \quad n = 1, \ldots, e-1. \tag{24}
\]

The result of the extrapolation provides an accurate initial condition \( a_{n+1,0} \) for the next finite element and polynomial \( \tilde{u}(\zeta_{n+1}) \).

The optimization problem given in Eq. (1) can now be solved easily with any solver. For the example metabolic network, the linear programming (LP) formulation described in Eq. (2) including the ODEs discretized on finite elements and the
orthogonal roots are shown in Table 1.

Objective:

\[
\max \sum E(t_{n,i}) \quad n = 1, \ldots, 3 \quad i = 1, \ldots, 5
\]

s.t.

\[
A(t_{1,0}) = A_0 = 2
\]

\[
B(t_{1,0}) = B_0 = 2
\]

\[
C(t_{1,0}) = C_0 = 2
\]

\[
E(t_{1,0}) = E_0 = 2
\]

\[
0 = A(t)^L \leq A(t) \leq A(t)^U = 100
\]

\[
0 = B(t)^L \leq B(t) \leq B(t)^U = 100
\]

\[
0 = C(t)^L \leq C(t) \leq C(t)^U = 100
\]

\[
0 = E(t)^L \leq E(t) \leq E(t)^U = 100
\]

\[
0 = v_m(t)^L \leq v_m(t) \leq v_m(t)^U = 100 \quad m = 1, \ldots, 3,
\]

\[
\forall n, i \quad 1 \leq n \leq 3, \quad 1 \leq i \leq 5
\]

\[
R_A(t_{n,i}) = \frac{d\hat{A}(t_{n,i})}{dt} - \frac{d\overline{A}(t_{n,i})}{dt} = \sum_{j=1}^{K} A_{n,j} \cdot \hat{\phi}_j(t_{n,i}) - (v_{1,n,i}) = 0
\]

\[
R_B(t_{n,i}) = \frac{d\hat{B}(t_{n,i})}{dt} - \frac{d\overline{B}(t_{n,i})}{dt} = \sum_{j=1}^{K} B_{n,j} \cdot \hat{\phi}_j(t_{n,i}) - (v_{1,n,i} + v_{2,n,i}) = 0
\]

\[
R_C(t_{n,i}) = \frac{d\hat{C}(t_{n,i})}{dt} - \frac{d\overline{C}(t_{n,i})}{dt} = \sum_{j=1}^{K} C_{n,j} \cdot \hat{\phi}_j(t_{n,i}) - (-v_{1,n,i} + v_{2,n,i}) = 0
\]

\[
R_E(t_{n,i}) = \frac{d\hat{E}(t_{n,i})}{dt} - \frac{d\overline{E}(t_{n,i})}{dt} = \sum_{j=1}^{K} E_{n,j} \cdot \hat{\phi}_j(t_{n,i}) - (-2v_{2,n,i} + v_{3,n,i}) = 0
\]

\[
\forall n \quad n = 1
\]

\[
\sum_{j=1}^{K} A_{n,j} \cdot \phi_j(0) - A_0 = 0
\]

\[
\sum_{j=1}^{K} B_{n,j} \cdot \phi_j(0) - B_0 = 0
\]

\[
\sum_{j=1}^{K} C_{n,j} \cdot \phi_j(0) - C_0 = 0
\]

\[
\sum_{j=1}^{K} E_{n,j} \cdot \phi_j(0) - E_0 = 0
\]

\[
\forall n \quad 2 \leq n \leq 3
\]

\[
\sum_{j=1}^{K} A_{n-1,j} \cdot \phi_j(1) - \sum_{j=1}^{K} A_{n,j} \cdot \phi_j(0) = 0
\]

\[
\sum_{j=1}^{K} B_{n-1,j} \cdot \phi_j(1) - \sum_{j=1}^{K} B_{n,j} \cdot \phi_j(0) = 0
\]

\[
\sum_{j=1}^{K} C_{n-1,j} \cdot \phi_j(1) - \sum_{j=1}^{K} C_{n,j} \cdot \phi_j(0) = 0
\]

\[
\sum_{j=1}^{K} E_{n-1,j} \cdot \phi_j(1) - \sum_{j=1}^{K} E_{n,j} \cdot \phi_j(0) = 0,
\]

where \(A_{n,i}, B_{n,i}, C_{n,i}\) and \(E_{n,i}\) are the concentrations of each metabolite and \(v_{1,n,i}, v_{2,n,i}\) and \(v_{3,n,i}\) are the reaction rates at time points (collocation points) \(t_{n,i}\), \(1 \leq n \leq 3, \ 1 \leq i \leq 5\), respectively. The solution of the coefficients at the orthogonal roots are shown in Table 1.
<table>
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<tr>
<th>Coefficients at orthogonals roots</th>
<th>Metabolites</th>
<th>Reactions</th>
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<td>89.3620</td>
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Table 1: Results of metabolite concentrations and reaction rates at different orthogonal roots. The LP problem given in Eq. (25) was solved by the linprog function in MATLAB.

References


