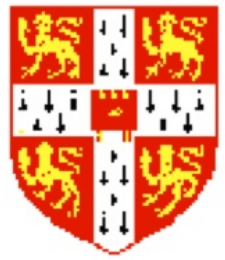
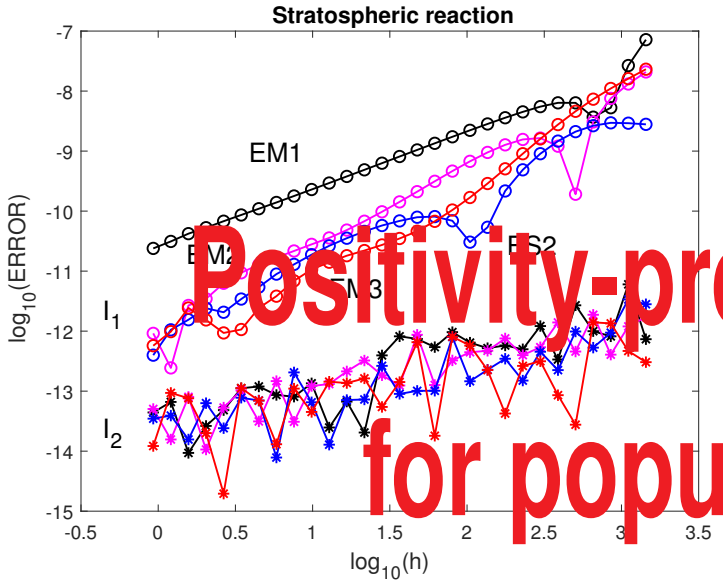
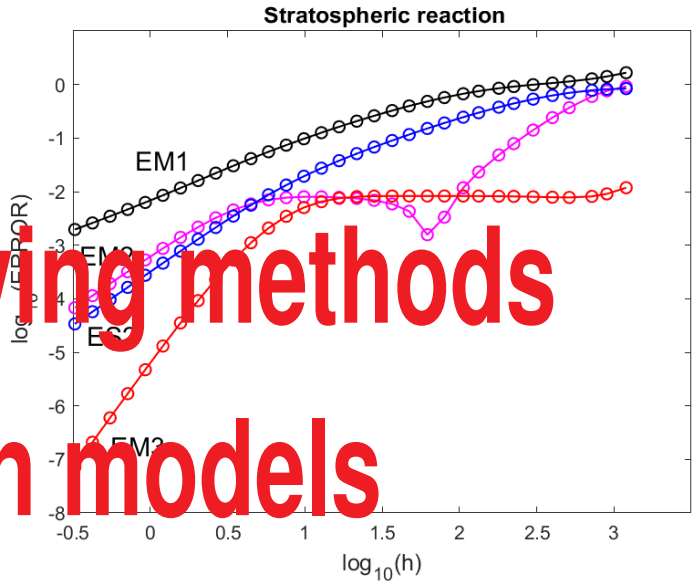


UNIVERSITY OF CAMBRIDGE

CENTRE FOR MATHEMATICAL SCIENCES

DEPARTMENT OF APPLIED MATHEMATICS
& THEORETICAL PHYSICS





Positivity-preserving methods for population models

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February 2021

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I. The setting

Numerous problems in population dynamics, chemical reactions, biochemical systems and epidemiology can be formulated as ODEs

$$\boldsymbol{y}' = \boldsymbol{f}(t, \boldsymbol{y}), \qquad \boldsymbol{y}(0) = \boldsymbol{y}_0 \in \mathbb{R}^d,$$

with two features:

- **Mass preservation:** $\sum_{i=1}^{d} y_i(t) \equiv \text{const.}$;
- **Positivity preservation:** $y_1(t), \ldots, y_d(t) \geq 0$.

These features are explained by another one:

- **Graph Laplacian:** $\boldsymbol{f}(t, \boldsymbol{y}) = A(t, \boldsymbol{y})\boldsymbol{y}$, where A is a graph Laplacian matrix:

$$A_{k,k} \leq 0, \qquad A_{k,\ell} \geq 0, \quad \ell \neq k, \qquad k, \ell = 1, \ldots, d$$

and

$$\sum_{k=1}^{d} A_{k,\ell} = 0, \qquad \ell = 1, \ldots, d.$$

It is instructive to persuade ourselves that the solution of $\boldsymbol{y}' = A(\boldsymbol{y})\boldsymbol{y}$, where A is a graph Laplacian, conserves both mass and positivity. The first is trivial:

$$\mathbf{1}^\top \boldsymbol{y}'(t) = \mathbf{1}^\top A(\boldsymbol{y}(t))\boldsymbol{y}(t) = \mathbf{0}^\top \boldsymbol{y}(t) = 0.$$

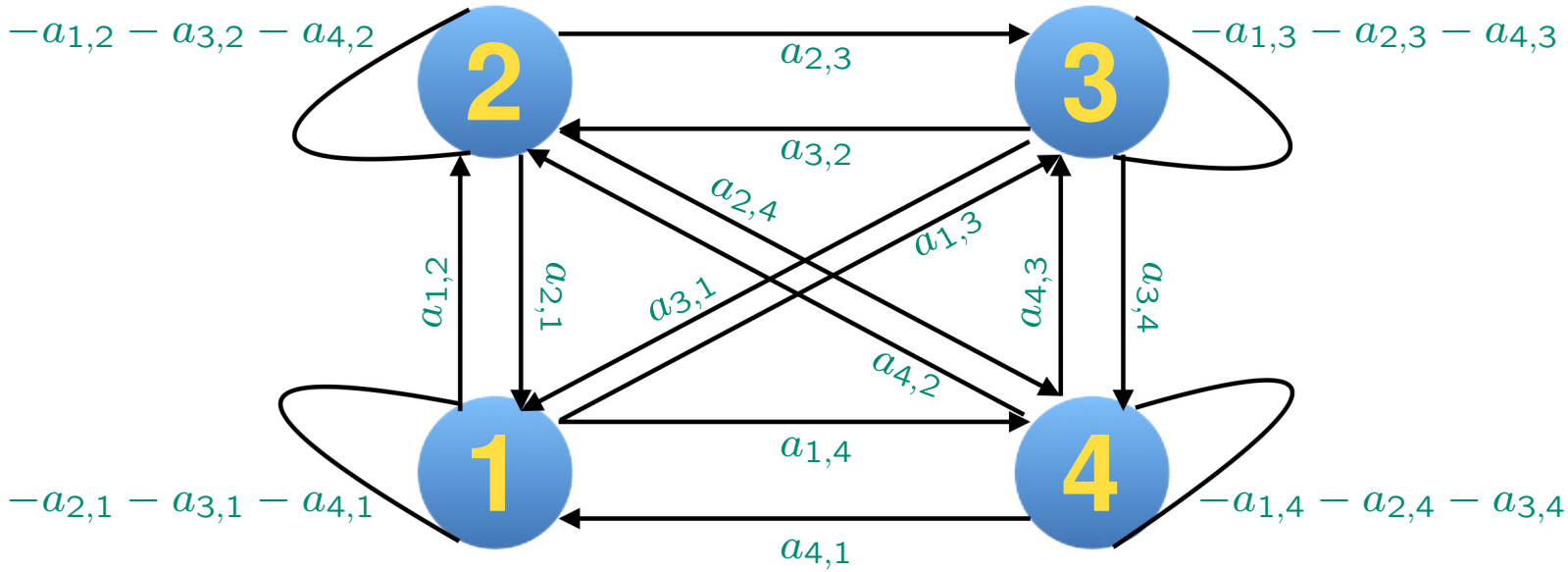
Suppose that $\exists t^* > 0$ s.t. $y_{k^*}(t^*) = 0$ for some k^* and $\boldsymbol{y}(t^*) \succeq \mathbf{0}$. Then

$$y'_{k^*}(t^*) = \sum_{\ell=1}^{d} A_{k^*,\ell}(\boldsymbol{y}(t^*))y_\ell(t^*) = \sum_{\ell \neq k^*} A_{k^*,\ell}(\boldsymbol{y}(t^*))y_\ell(t^*) \geq 0,$$

because $A_{k^*,\ell} \geq 0$ for $\ell \neq k^*$. Hence preservation of positivity.

But. . . **Why are such equations important?**

Kirkhoff 1st law: A reason for the ubiquity of graph Laplacians is the Kirkhoff law for networks. Consider the directed graph corresponding to a 4×4 matrix A:



In other words, 'charge' is conserved in a network.

Probability vectors: An alternative explanation is that y_0 is a probability vector once $y_0 \succeq 0$ and $1^\top y_0 \equiv 1$. In a graph Laplacian system this remains true for $y(t)$ for all t – and this, typically, is a major structural feature of the biological or chemical system being modelled.

Example 1: The Robertson reaction. This is chemical reaction $A \to B$, $B + B \to B + C \to A + C$ resulting in stiff ODEs for the concentrations of A, B, C,

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix} = \begin{bmatrix} -0.04 & 10^4 y_3 & 0 \\ 0.04 & -3 \cdot 10^7 y_2 - 10^4 y_3 & 0 \\ 0 & 3 \cdot 10^7 y_2 & 0 \end{bmatrix} \begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix}.$$

This is not the only way of writing the Robertson reaction in the form $y' = A(y)y$ – but it is the correct one! We'll return to this issue later...

Example 2: The SIR model of Kermack & McKendrick models the spread of epidemics:

$$S' = -R_0 SI, \qquad I' = R_0 SI - I, \qquad R' = I,$$

and can be written in a graph-Laplacian form with polynomial A.

Example 3: The Michaelis–Menten equations of enzyme dynamics can be written in the form $\boldsymbol{y}' = A\boldsymbol{y}$, where A is a constant graph Laplacian matrix.

Numerous other examples modelling cardiac ion channels, G-protein coupled receptors, gene regulation, MAPK (mitogen-activated protein kinase) cascade and more.

We need to preserve two features:

- **Mass preservation** $1^\top y(t) \equiv 1$ – this is easy: all nontrivial multistep or Runge–Kutta methods do it.
- **Positivity** $y(t) \succeq 0$ – this is exceedingly difficult. According to a result of Boley & Crouzeix a convergent multistep method preserving positivity must be of order 1, e.g. backward Euler.*

Our main purpose in this talk is to introduce higher-order ODE methods that tick both boxes. A secondary purpose is to identify ODE systems that can be written in the form $y' = A(y)y$, where A is a graph Laplacian with polynomial entries.

*Strictly speaking, they proved it for semidiscretised parabolic PDEs, but similar proof is valid in greater generality.

II. Constant graph Laplacians

Suppose that A is a constant (and also graph Laplacian). The exact solution of $\boldsymbol{y}' = A\boldsymbol{y}$ is $\boldsymbol{y}(t) = \mathrm{e}^{tA}\boldsymbol{y}_0$.

Theorem *Let A be a (constant) graph Laplacian. Then it has an eigenvalue at the origin, which is simple if A is irreducible, and all its other eigenvalues live in $\mathbb{C}^-$.*

Proof $\mathbf{1}^\top A = \mathbf{0}^\top$ implies that $0 \in \sigma(A)$, while the location of the remaining eigenvalues in the left half-plane follows from the Gerschgorin theorem applied to the *columns* of A. To prove that 0 is a simple eigenvalue, we set $\alpha = \min_k A_{k,k}$ and observe that $B = A - \alpha I \succeq O$. Using the Perron–Frobenius theory of positive matrices, we deduce simplicity of the largest eigenvalue when A is irreducible. □

Corollary $\mathbf{1}^\top \mathrm{e}^{tA} = \mathbf{1}^\top$.

Lemma *If A is a graph Laplacian then $\mathrm{e}^{tA} \succ O$ for all $t \geq 0$.*

Proof Set again $\alpha = \min_k A_{k,k} < 0$ and $B = A - \alpha I$. Then

$$\mathrm{e}^{tA} = \mathrm{e}^{t\alpha + tB} = \mathrm{e}^{t\alpha}\mathrm{e}^{tB} \succ O$$

because $B \succeq O$ implies $\mathrm{e}^{tB} = \sum_{n=0}^{\infty} \frac{1}{n!} t^n B^n \succ O$. □

Solving $y' = Ay$: We just compute the exponential. For large d we can replace it by a rational approximation r as long as $r(tA) \succ O$, e.g.

$$r(z) = \frac{1 + \frac{1}{2}z + \frac{1}{12}z^2}{1 - \frac{1}{2}z + \frac{1}{12}z^2} = \mathrm{e}^z + \mathcal{O}\left(z^5\right).$$

Alternatively, we can approximate A by a smaller $\tilde{A}$, as long as the latter is itself a graph Laplacian. But careful:

$$r(z) = 1 + z + \frac{z^2}{2} + \frac{z^3}{6} + \frac{z^4}{24} + \frac{z^5}{144} - \frac{z^7}{1728} + \cdots$$

III. Non-autonomous systems

Suppose that $\boldsymbol{y}' = A(t)\boldsymbol{y}$, where $A(t)$ is a graph Laplacian. The solution can be written in the form $\boldsymbol{y}(t) = \mathrm{e}^{\Omega(t)}\boldsymbol{y}(0)$, where Ω can be obtained by Magnus expansion Blanes & Casas; AI, Munthe-Kaas, Nørsett & Zanna):

$$\Omega(t) = \int_{t_n}^{t} A(\tau)\,\mathrm{d}\tau - \frac{1}{2}\int_{t_n}^{t}\int_{t_n}^{\tau}[A(\tau), A(\eta)]\,\mathrm{d}\eta\,\mathrm{d}\tau + \cdots.$$

Truncation of the infinite expansion results in

2nd order method: $\Omega(t) \approx \int_{t_n}^{t} A(\tau)\,\mathrm{d}\tau,$

4th order method: $\Omega(t) \approx \int_{t_n}^{t} A(\tau)\,\mathrm{d}\tau - \frac{1}{2}\int_{t_n}^{t}\int_{t_n}^{\tau}[A(\tau), A(\eta)]\,\mathrm{d}\eta\,\mathrm{d}\tau$

and so on – there are known ways of attaining an arbitrary even order and cheap means of evaluating underlying integrals:

2nd order: $\boldsymbol{y}_{n+1} = \exp\Big(hA(t_n + \frac{1}{2}h)\Big)\boldsymbol{y}_n,$

4th order: $\boldsymbol{y}_{n+1} = \exp\Big(\frac{1}{2}h(\mathcal{B}_1 + \mathcal{B}_2) + \frac{\sqrt{3}}{12}h^2[\mathcal{B}_1, \mathcal{B}_2]\Big)\boldsymbol{y}_n,$

$$\mathcal{B}_1 = A(t_n + (\tfrac{1}{2} - \tfrac{\sqrt{3}}{6})h), \qquad \mathcal{B}_2 = A(t_n + (\tfrac{1}{2} + \tfrac{\sqrt{3}}{6})h).$$

$\mathcal{B}_1$ and $\mathcal{B}_2$ are graph Laplacians – but not necessarily $[\mathcal{B}_1, \mathcal{B}_2]$. An alternative: commutator-free Magnus (Blanes, Casas & Thalhammer). A 4th-order method is given by

$$\boldsymbol{y}_{n+1} = \exp\Big(\frac{h}{2}(\beta\mathcal{B}_1 + \alpha\mathcal{B}_2)\Big)\exp\Big(\frac{h}{2}(\alpha\mathcal{B}_1 + \beta\mathcal{B}_2)\Big)\boldsymbol{y}_n,$$

where

$$\alpha = \frac{1}{2} - \frac{\sqrt{3}}{3}, \qquad \beta = \frac{1}{2} + \frac{\sqrt{3}}{3}.$$

Since $\alpha < 0$, the arguments of the exponentials need not be graph Laplacians – but $\beta/|\alpha| \approx 14$ hence, unless A changes rapidly in the interval, all is well!

IV. Polynomial systems

We are concerned with $\boldsymbol{y}' = A(t, \boldsymbol{y})\boldsymbol{y}$, where A is a graph Laplacian and each $A_{k,\ell}(\boldsymbol{y})$ is a polynomial in $y_1, \ldots, y_d$. We can leverage the solution of linear systems to this setting by iteration:

$$\begin{aligned} \boldsymbol{y}^{[0]} &\equiv \boldsymbol{y}_0, \\ \boldsymbol{y}^{[m+1]\prime} &= A(\boldsymbol{y}^{[m]}(t))\boldsymbol{y}^{[m+1]}, \ \ \boldsymbol{y}^{[m+1]}(t_n) = \boldsymbol{y}_n, \quad m = 0, \ldots, m^* - 1, \\ \boldsymbol{y}_{n+1} &= \boldsymbol{y}^{[m^*]}(t_{n+1}). \end{aligned}$$

Each iteration involves the solution of a non-autonomous linear system – and this can be done with a 2nd-order method preserving mass and positivity (and with a 4th-order method *almost* doing so). Since each iteration increases order, for 2nd order we need $m^* = 2$.

We have

$$\boldsymbol{y}^{[1]}(t) = \mathrm{e}^{tA(\boldsymbol{y}_n)}\boldsymbol{y}_n,$$
$$\boldsymbol{y}^{[2]}(t) \approx \exp\left(\int_{t_n}^{t} A(\mathrm{e}^{(\tau-t_n)A(\boldsymbol{y}_n)}\boldsymbol{y}_n)\,\mathrm{d}\tau\right)\boldsymbol{y}_n,$$

hence the 2nd-order method

$$\boldsymbol{y}_{n+1} = \exp\left(hA(\mathrm{e}^{\frac{1}{2}hA(\boldsymbol{y}_n)}\boldsymbol{y}_n\right)\boldsymbol{y}_n.$$

Note that $\boldsymbol{y}_n \succeq 0$, $\mathbf{1}^\top \boldsymbol{y}_n = 1$ is inherited by $\boldsymbol{y}_{n+1}$, as required.

And this is as much as we can do preserving both mass and positivity – still better than the Boley–Crouzeix first-order barrier!

Yet, it is interesting to explore higher-order methods that *almost always* preserve mass and positivity.

A 4th-order Magnus integrator Recall that 4th-order Magnus for $A = \tilde{A}(t)$ is

$$\boldsymbol{y}_{n+1} = \exp\left(\frac{h}{2}(\mathcal{B}_1 + \mathcal{B}_2) + \frac{\sqrt{3}}{12}h^2[\mathcal{B}_1, \mathcal{B}_2]\right)\boldsymbol{y}_n,$$

where

$$\mathcal{B}_1 = \tilde{A}(t_n + (\tfrac{1}{2} - \tfrac{\sqrt{3}}{6})h), \qquad \mathcal{B}_2 = \tilde{A}(t_n + (\tfrac{1}{2} + \tfrac{\sqrt{3}}{6})h),$$

except that in the current case

$$\tilde{A}(t) = A\left(\exp\left(\int_{t_n}^{t} A(\eta)\,\mathrm{d}\eta\right)\boldsymbol{y}_n\right).$$

A 4th-order approximation (including a quadrature of the integral in $\tilde{A}$ is

$$\mathcal{B}_1 = A\left(\exp\left((\tfrac{1}{4} - \tfrac{\sqrt{3}}{12}h)h\left[A(t_n + (\tfrac{1}{3} - \tfrac{\sqrt{3}}{6})h) + A(t_n + \tfrac{1}{6}h)\right]\right)\boldsymbol{y}_{n+1}\right),$$

$$\mathcal{B}_2 = A\left(\exp\left((\tfrac{1}{4} + \tfrac{\sqrt{3}}{12}h)h\left[A(t_n + \tfrac{1}{6}h) + A(t_n + (\tfrac{1}{3} + \tfrac{\sqrt{3}}{6})h)\right]\right)\boldsymbol{y}_{n+1}\right).$$

While $\mathcal{B}_1, \mathcal{B}_2$ are graph Laplacians, this property might be lost by $[\mathcal{B}_1, \mathcal{B}_2]$ – thus, the method *mostly* works but it is possible to generate counterexamples.

An alternative is provided by commutator-free methods: again, we obtain a 2nd-order method which is assured to preserve both mass and positivity, as well as almost-preserving 3rd and 4th-order methods.

Conjecture *The highest order of a method which preserves both mass and positivity for $\boldsymbol{y}' = A(\boldsymbol{y})\boldsymbol{y}$ within the family of Magnus-like methods is two.*

V. Identifying polynomial systems

Suppose we have an ODE system

$$y_k' = \sum_{j=1}^{m} \sum_{\substack{\ell_1+\cdots+\ell_d=j \\ \ell_1,\ldots,\ell_d\geq 0}} a_k^{\ell_1,\ldots,\ell_d} y_1^{\ell_1}\cdots y_d^{\ell_d} = \sum_{j=1}^{m} \sum_{|\boldsymbol{\ell}|=j} a_k^{\boldsymbol{\ell}} \boldsymbol{y}^{\boldsymbol{\ell}}$$

for $k = 1, \ldots, d$. Can it be written in the form

$$\boldsymbol{y}' = A(\boldsymbol{y})\boldsymbol{y},$$

where $A(\boldsymbol{y})$ is a graph Laplacian?

Such representation need not be unique. E.g., for $d = 2,\ j = 2$ we have

$$y_k' = a_k^{1,1} y_1^2 + (a_k^{1,2} + a_k^{2,1}) y_1 y_2 + a_k^{2,2} y_2^2, \qquad k = 1, 2,$$

therefore

$$A(\boldsymbol{y}) = \begin{bmatrix} a_1^{1,1} y_1 + \beta_{1,1} y_2 & \beta_{1,2} y_1 + a_1^{2,2} y_2 \\ a_2^{1,1} y_1 + \beta_{2,1} y_2 & \beta_{2,2} y_1 + a_2^{2,2} y_2 \end{bmatrix},$$

$$\beta_{k,1} + \beta_{k,2} = a_k^{1,2} + a_k^{2,1}, \qquad k = 1, 2.$$

The conditions for a graph Laplacian (for every $\boldsymbol{y} \succeq \mathbf{0}$) are

$$a_1^{1,1}, a_2^{2,2}, \beta_{1,1}, \beta_{2,2} \leq 0,$$
$$a_1^{1,1} + a_2^{1,1} = a_1^{2,2} + a_2^{2,2} = \beta_{1,1} + \beta_{2,1} = \beta_{1,2} + \beta_{2,2} = 0.$$

Six equalities and four equalities for eight variables. Hence in some configurations there are no graph Laplacian solutions, in others we might have an infinity of such solutions.

A simplification: it is enough to write

$$y'_k = \sum_{|\boldsymbol{\ell}|=j} a_k^{\boldsymbol{\ell}} \boldsymbol{y}^{\ell}, \quad k = 1, \ldots, d \qquad \text{as} \qquad \boldsymbol{y}' = A_j(\boldsymbol{y})\boldsymbol{y},$$

whereby (for the full system) $\boldsymbol{y}' = [A_1(\boldsymbol{y}) + \cdots + A_m(\boldsymbol{y})]\boldsymbol{y}$.

The case $j = 1$ is trivial, we now focus on $j = 2$.

We thus consider

$$y_k' = \sum_{|\ell|=2} a_k^{\sum_{i=1}^d \ell_i \boldsymbol{e}_i} y_1^{\ell_1} y_2^{\ell_2} \cdots y_d^{\ell_d},$$

where $\boldsymbol{e}_i$ is the ith unit vector.

Theorem *The above system admits a graph Laplacian representation if*

$$a_k^{2\boldsymbol{e}_k} \le 0, \qquad a_k^{2\boldsymbol{e}_i} \ge 0, \qquad k, i = 1, \ldots, d, \quad i \ne k, \tag{1}$$

$$a_k^{\boldsymbol{e}_i + \boldsymbol{e}_k} \le 0, \quad a_k^{\boldsymbol{e}_i + \boldsymbol{e}_j} \ge 0, \qquad k, i, j = 1, \ldots, d, \quad i \ne j, \quad k \ne i, j, \tag{2}$$

$$\sum_{k=1}^d a_k^{\boldsymbol{e}_k + \boldsymbol{e}_i} = 0, \qquad i = 1, \ldots, d. \tag{3}$$

Proof We construct a graph Laplacian $A(\boldsymbol{y})$ explicitly:

$$A_{k,\ell}(\boldsymbol{y}) = a_k^{2\boldsymbol{e}_\ell} y_\ell + a_k^{\boldsymbol{e}_\ell + \boldsymbol{e}_{\ell+1}} y_{\ell+1}, \qquad k, \ell = 1, \ldots, d \pmod{d}.$$

To prove that it is a graph Laplacian:

$$A_{k,k}(\boldsymbol{y}) = a_k^{2\boldsymbol{e}_k} y_k + a_k^{\boldsymbol{e}_k + \boldsymbol{e}_{k+1}} y_{k+1} \pmod{d} \le 0,$$

because $\boldsymbol{y} \succeq \boldsymbol{0}$ and (1–2). For the same reason

$$A_{k,\ell}(\boldsymbol{y}) = a_k^{2\boldsymbol{e}_\ell} y_\ell + a_k^{\boldsymbol{e}_\ell + \boldsymbol{e}_{\ell+1}} y_{\ell+1} \pmod{d} \ge 0, \qquad k \ne \ell.$$

Finally, (3) implies that

$$\sum_{k=1}^{d} A_{k,\ell}(\boldsymbol{y}) = \left(\sum_{k=1}^{d} a_k^{2\boldsymbol{e}_\ell} \right) y_\ell + \left(\sum_{k=1}^{d} a_k^{\boldsymbol{e}_\ell + \boldsymbol{e}_{\ell+1}} \right) y_{\ell+1} \pmod{d} = 0$$

and we are done. □

A general theory for $j \ge 3$ is unavailable.

VI. Examples

Chemical reactions by the Law of Mass Action. We have chemical species $G_1, \ldots, G_M$: y_i is the concentration of G_i, while $r_{i,j}, q_{i,j} \geq 0$ are integer coefficients. The jth reaction is

$$r_{j,1}G_1 + \cdots + r_{j,M}G_m \xrightarrow{k_j} q_{j,1}G_1 + \cdots, q_{j,M}G_M,$$

where $k_j > 0$ is the rate constant. The ODE governing this process is

$$\boldsymbol{y}' = S\boldsymbol{p}, \quad \boldsymbol{y}(0) = \boldsymbol{y}_0 \succeq \boldsymbol{0},$$

where $S_{i,j} = q_{i,j} - r_{i,j}$ is the stoichiometric matrix and

$$p_j = k_j \prod_{i=1}^{M} y_i^{r_{i,j}}$$

is the Law of Mass Action. (It might be non-autonomous if $k_j = k_j(t)$.) The ODE can be written in the form $\boldsymbol{y}' = A(\boldsymbol{y})\boldsymbol{y}$.

Lemma *Negative elements of $A(\boldsymbol{y})$ may appear only along its diagonal.*

The proof of the lemma is constructive.

In other words, the ODE preserves positivity. It need not preserve mass but all our methods preserve just positivity on its own! This is an important issue because many interesting ODEs of chemistry and population dynamics maintain positivity but fall short of conserving mass.

Robertson's reaction. Recall that

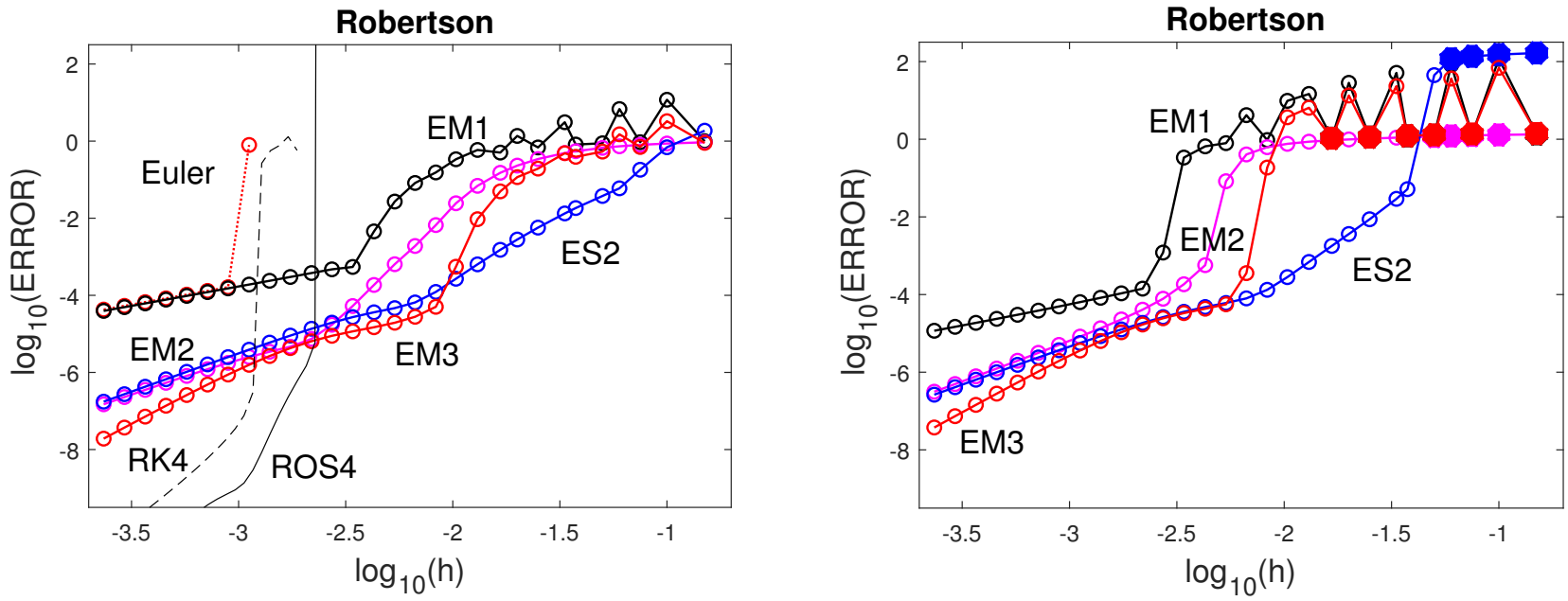
$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix} = \begin{bmatrix} -0.04 & 10^4 y_3 & 0 \\ 0.04 & -3\cdot 10^7 y_2 - 10^4 y_3 & 0 \\ 0 & 3\cdot 10^7 y_2 & 0 \end{bmatrix}\begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix}$$

and set $\boldsymbol{y}_0 = [1, 0, 0]^\top$.

We consider

- **ES2**: Symmetric 2nd-order 3-exponential splitting,
- **EM1**: 1st-order, 1-exponential Euler-Magnus,
- **EM2**: 2nd-order, 2-exponential commutator-free Magnus,
- **EM3**: 3rd-order, 7-exponential commutator-free Magnus;
- **Euler**: 1st-order explicit Euler,
- **RK4**: 4th-order 4-stage explicit RK,
- **ROS4:** 4th-order 4-stage Rosenbrock method.

We applied this both to the above Robertson equation and to its alternative formulation $y' = A(y)y$ where A is not a graph Laplacian. A circle $\circ$ corresponds to all nonnegative values, $\bullet$ to a step size s.t. the solution fails the positivity test.



On the left: graph-Laplacian $A(\boldsymbol{y})$; on the right: another choice of $A(\boldsymbol{y})$. Error at $\frac{3}{10}$ with different step sizes. The slopes reflect the order – but note that **Euler**, **RK4** and **ROS4** break down unless h is small. (And they are independent of the form of $A(\boldsymbol{y})$, hence appear only on the left.)

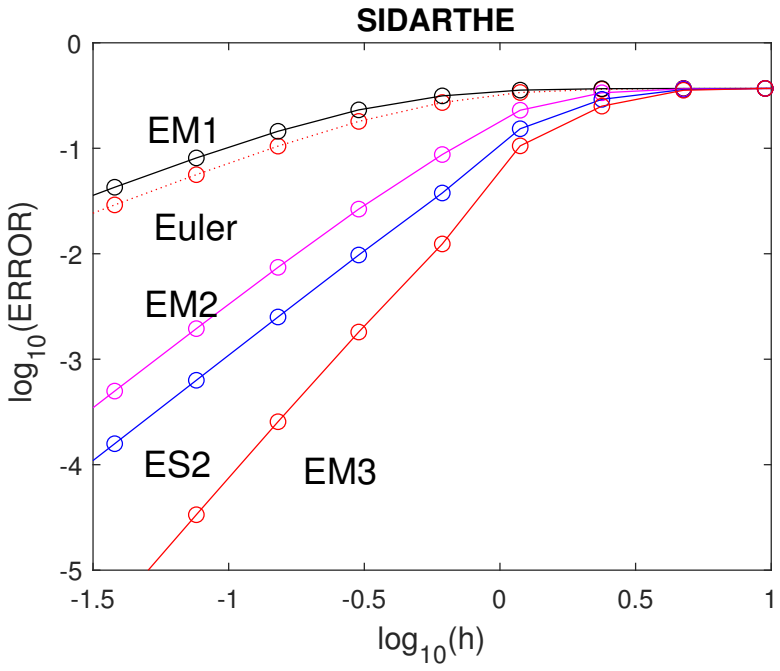
The SIDARTHE model. This are generalised SIR equations that has been used to model the Cov-SARS-2 epidemic in Italy over 46 days in Winter 2020:

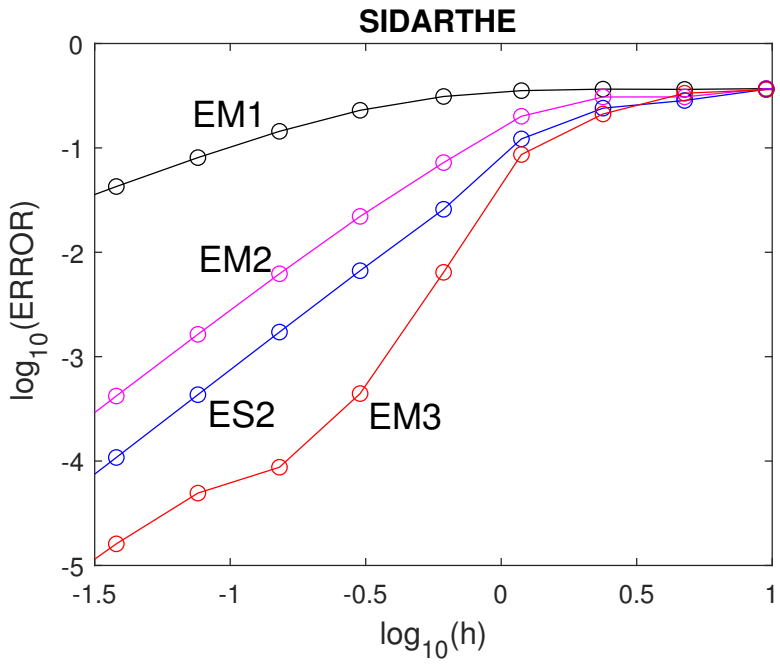
$$\boldsymbol{y}' = A(\boldsymbol{b}(t), \boldsymbol{y})\boldsymbol{y}, \qquad \boldsymbol{y}(0) \in \mathbb{R}^8,$$

where $\boldsymbol{b}(t) \in \mathbb{R}^{15}$ is a time-dependent piecewise-constant vector of parameters. The aim was to establish the impact of progressive restrictions on the spread of the virus.

Given the size of the system (and the wish to apply to much larger systems) we explore two options:

- Evaluating the matrix exponential exactly; and
- Replacing it by $[1/1]$ Padé approximation – it is of order 2 but preserves both mass and positivity.





In double-log scale: on the left exact computation of the exponential (irrelevant for **Euler**) and on the right a Padé approximation. Strangely, using Padé does not degrade the solution, except for **EM3** for a very small step size – understandable because Padé $[1/1]$ is just 2nd -order!

The stratopheric reaction Six unknowns corresponding to ions of gases in the stratosphere and

$$
\begin{aligned}
y_1' &= k_5 y_3 - k_6 y_1 - k_7 y_1 y_3, \\
y_2' &= 2k_1 y_4 - k_2 y_2 y_4 + k_3 y_3 - k_4 y_2 y_3 + k_6 y_1 - k_9 y_2 y_6 + k_{10} y_6, \\
y_3' &= k_2 y_2 y_4 - k_3 y_3 - k_4 y_2 y_3 - k_5 y_3 - k_7 y_1 y_3 - k_8 y_3 y_5, \\
y_4' &= -k_1 y_4 - k_2 y_2 y_4 + k_3 y_3 + 2k_4 y_2 y_3 + k_5 y_3 + 2k_7 y_1 y_3 + k_8 y_3 y_5 + k_9 y_2 y_6, \\
y_5' &= -k_8 y_3 y_5 + k_9 y_2 y_6 + k_{10} y_6, \\
y_6' &= k_8 y_3 y_5 - k_9 y_2 y_6 - k_{10} y_6,
\end{aligned}
$$

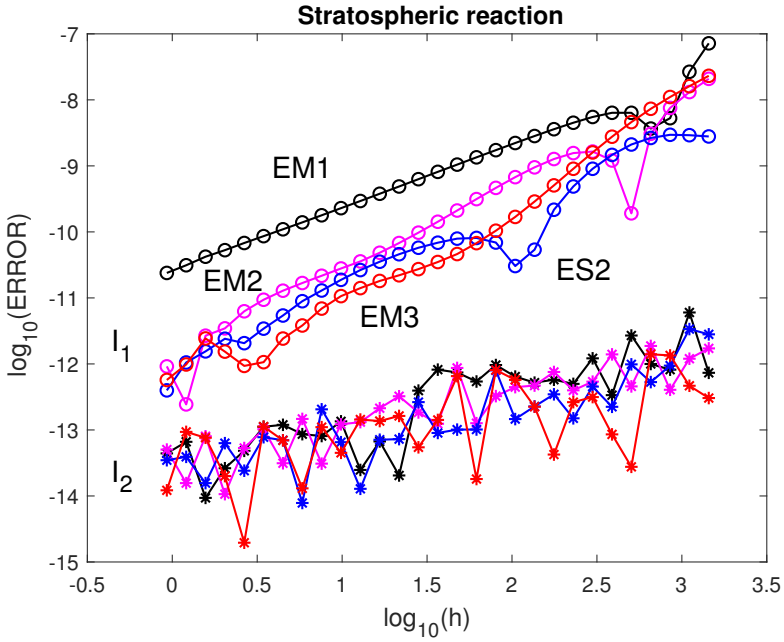
where $\sigma(t)$ is given. This can be written in the form $\boldsymbol{y}' = A(t, \boldsymbol{y})\boldsymbol{y}$.

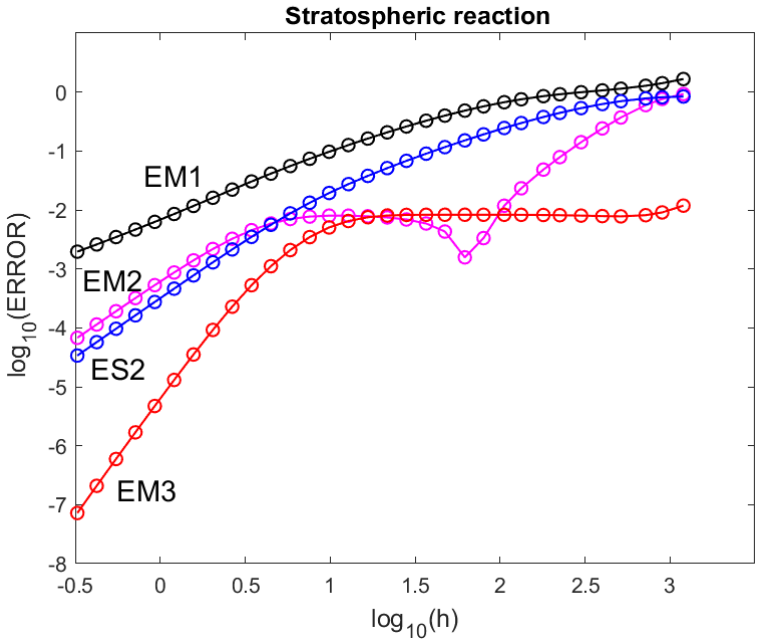
The problem has two linear conservation laws, $\boldsymbol{w}_i^\top \boldsymbol{y}(t) = \text{const}$, $i = 1, 2$, where $\boldsymbol{w}_1 = [1, 1, 2, 3, 1, 2]^\top$, $\boldsymbol{w}_2 = [0, 0, 0, 0, 1, 1]^\top$. However, there exists no $A(\boldsymbol{y})$ s.t. $\boldsymbol{w}_i^\top A(\boldsymbol{y})\boldsymbol{y} = 0$, $i = 1, 2$, so we enforce only $\boldsymbol{w}_2$, while choosing $A(\boldsymbol{y})$ s.t. $\boldsymbol{w}_1$ is almost satisfied.

Let $A(\boldsymbol{y})$ be

$$\begin{bmatrix} -(k_6+k_7y_3) & 0 & k_5 & 0 & 0 & 0 \\ k_6 & -(k_2y_4+k_4y_3+k_9y_6) & k_3 & 2k_1 & 0 & k_{10} \\ 0 & \frac{1}{3}k_2y_4 & -(k_3+k_5+k_4y_3+k_7y_1+k_8y_5) & \frac{2}{3}k_2y_2 & 0 & 0 \\ \frac{1}{2}k_7y_3 & k_4y_3+\frac{1}{2}k_9y_6 & k_3+k_5+k_4y_3+\frac{3}{2}k_7y_1+k_8y_5 & -(k_1+k_2y_2) & 0 & \frac{1}{2}k_9y_2 \\ 0 & 0 & 0 & 0 & -k_8y_3 & k_{10}+k_9y_2 \\ 0 & 0 & 0 & 0 & k_8y_3 & -(k_{10}+k_9y_2) \end{bmatrix}.$$

$A(\boldsymbol{y})$ is not a graph Laplacian! In place of mass conservation, we have $I_2 = \boldsymbol{w}_2^\top \boldsymbol{y}(t) \equiv \text{const}$, while $I_1 = \boldsymbol{w}_1^\top \boldsymbol{y}(t)$ is *almost* constant (i.e. its variation is significantly smaller than the numerical error). Moreover, for all $\boldsymbol{y} \succeq \boldsymbol{0}$ $A_{k,k}(\boldsymbol{y}) \leq 0$, $A_{k,\ell}(\boldsymbol{y}) \geq 0$ for $k \neq \ell$, hence positivity is guaranteed and our methods preserve it.





On the left: The error in preserved quantities I_1, I_2 – note that the error in I_2 is essentially roundoff. On the right: The ℓ_2 error at one hour ($t_f = 3600$) vs the time step in double-log scale. Note that the sign never changes and the higher-order method, **EM3**, is a clear winner.

VII. Take-home lessons

- While our point of departure was ODEs originating in population dynamics, the basic structure – polynomial equations, mass conservation and positivity – are important in much wider range of applications in biology and chemistry – **and we didn't even mention the master equations**, describing probabilistic combination of states in physics, biology and chemistry!

- Graph Laplacians are an important unifying structural feature but many equations require a relaxation of this concept.

- We can always resolve such equations while maintaining their invariants – but only up to order 2. (Even this is better than the Boley–Crozeix barrier!)

- We can ‘almost’ respect such invariants – and this works in practice – at least to order 3, probably higher.

- While such systems are not always written in the conservation form $\boldsymbol{y' = A(y)y}$, we have at least the beginning of a general theory how to write them in this manner.


THANK YOU
FOR
YOUR
ATTENTION!
ANY QUESTIONS?
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