

On Projection-Based Model Reduction of Biochemical Networks

Part I: The Deterministic Case

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Abstract—This paper addresses the problem of model reduction for dynamical system models that describe biochemical reaction networks. Inherent in such models are properties such as stability, positivity and network structure. Ideally these properties should be preserved by model reduction procedures, although traditional projection based approaches struggle to do this. We propose a projection based model reduction algorithm which uses generalised block diagonal Gramians to preserve structure and positivity. Two algorithms are presented, one provides more accurate reduced order models, the second provides easier to simulate reduced order models.

I. INTRODUCTION

Biochemical reaction networks are most appropriately modelled as stochastic systems. Typically they take the form of an infinite dimensional, continuous time Markov Chain which describes the time evolution of a probability density function of the number of molecules of the reactants. The Chemical Master Equation (CME)

$$\frac{\partial \mathbb{P}(n, t)}{\partial t} = \Omega \sum_{i=1}^R \hat{f}(n - S_i, \Omega) - \hat{f}(n, \Omega) \mathbb{P}(n, t)$$

describes how a reaction network composed of: R reactions, in a compartment of volume Ω with a stoichiometry matrix S (S_i denoting the i^{th} column); \hat{f} the flux vector; n the vector containing the number of molecules n_i of species i ; and $\mathbb{P}(n, t)$ is the probability of the vector of molecules n at time t changes with time.

For reaction networks with just a few species even simulating the CME can be intractable. This paper is a first step towards an automated procedure to compute efficient reduced order models for stochastic biochemical models. It is assumed that the starting point for the algorithms presented here is a nonlinear, possibly high dimensional, but deterministic dynamical system.

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The authors would like thank Prof Bayu Jayawardhana and Dr Shodhan Rao for kindly providing the kinetic model of yeast glycolysis. JA acknowledges funding through a junior research fellowship from St. Johns College, Oxford. AS is supported by the EPSRC Science and Innovation Award EP/G036004/1

Part 2 of this paper¹ [1] describes how and under what assumptions one can approximate the CME by a deterministic dynamical system.

The focus of this paper is to describe a projection based algorithm for reducing the state dimension of a dynamical system while preserving certain desirable features such as stability, positivity and network structure. Standard model reduction techniques make use of the fact that frequently states evolve over multiple time scales [2], [3].

More common in the control literature is the use of *projection* based model order reduction [4]–[7] which typically follows a two step procedure; first a state-space transformation is found which aligns the controllability and observability ellipsoids, then the states which are least controllable and observable are truncated yielding a reduced order model. In some cases, provided the initial full order model was stable it can be shown that the reduced model is stable too. It is often possible to *a priori* determine the error bound in an appropriate choice of norm between the full and reduced model. The major drawback of projection approaches is that the states in the transformed coordinate system are linear combinations of all the other states, thus the physical meaning of a state is lost. Recently structure preserving reduction algorithms have been proposed using structured Gramians [8], \mathcal{H}_∞ optimisation [9], [10] and novel energy functions [11] that attempt to avoid such problems. The work in this paper most closely resembles the spirit of [8], however in addition to preserving network structure would like to preserve the monotonicity, when possible.

II. PROBLEM STATEMENT

The standard model reduction problem takes the following form: given a stable dynamical system

$$\begin{aligned} \dot{x} &= f(x, u) \\ y &= h(x) \end{aligned} \quad (1)$$

where $x \in \mathbb{R}^n$ is the state vector, the equilibrium point of interest is without loss of generality $x_{ss} = 0_{n \times 1}$.

¹This paper is completely self-contained and does not require any of the material from Part II.

Construct a dynamical system

$$\begin{aligned}\dot{\tilde{x}} &= \tilde{f}(\tilde{x}, u) \\ \tilde{y} &= \tilde{h}(\tilde{x})\end{aligned}\quad (2)$$

where $\tilde{x} \in \mathbb{R}^k$ with $k < n$ and the *error* between (1)–(2) is small in some appropriate norm. When f is nonlinear the reduction problem is in general intractable, see [5], [6] for direct approaches. In this paper we shall deal with linearisations about a given operating point and input and adapt classical methods (cf. [12]) to preserve desirable system properties as outlined in the next section. In order to simplify some derivations, we assume that $h(x) = Cx$, where C is a constant matrix.

A. Structured Projectors

We approximate the system (1) around the stable steady-state x_{ss} with a constant control signal u_{ss} .

Consider a system

$$\begin{aligned}\dot{x} &= Ax + Bu \\ y &= Cx\end{aligned}\quad (3)$$

where the drift matrix A and input map B are given by

$$A = \left. \frac{\partial f(x, u)}{\partial x} \right|_{x=x_{ss}, u=u_{ss}}, \quad B = \left. \frac{\partial f(x, u)}{\partial u} \right|_{x=x_{ss}, u=u_{ss}}$$

Note that A is Hurwitz by assumption. The linearised system (3) can then be partitioned as follows:

$$x = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \quad A = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix} \quad B = \begin{pmatrix} B_1 \\ B_2 \end{pmatrix} \quad C^T = \begin{pmatrix} C_1^T \\ C_2^T \end{pmatrix}, \quad (4)$$

where $x_1 \in \mathbb{R}^{n-k}$, $x_2 \in \mathbb{R}^k$, and the matrices A , B and C are partitioned conformally. The next step is to compute structured (generalised) Gramians, which are obtained as solutions to Lyapunov inequalities

$$\begin{aligned}AP + PA^T + BB^T &\leq 0 \\ QA + A^T Q + C^T C &\leq 0\end{aligned}\quad (5)$$

with $P \geq 0$, $Q \geq 0$, subject to the same partitioning as the states:

$$P = \begin{pmatrix} P_{11} & 0_{n-k, k} \\ 0_{k, n-k} & P_{22} \end{pmatrix}, \quad Q = \begin{pmatrix} Q_{11} & 0_{n-k, k} \\ 0_{k, n-k} & Q_{22} \end{pmatrix}. \quad (6)$$

In the following section, we make a case why constraining the generalised Gramians P and Q to be block diagonal is not a restrictive assumption for biochemical networks.

If the states x_2 are to be approximated, the transformation T is composed as follows:

$$T = \begin{pmatrix} I_{n-k} & 0_{n-k, k} \\ 0_{n-k, k} & T_{22} \end{pmatrix}, \quad (7)$$

where T_{22} is such that

$$T_{22}^{-1} P_{22} T_{22}^{-T} = T_{22}^T Q_{22} T_{22} = \Sigma_{22},$$

and Σ_{22} is diagonal. According to standard tools [8], we choose the states to truncate according to the magnitude of the values of the diagonal of Σ_{22} . Assume r states are to be reduced, let W_{22} be the first $k-r$ columns of T_{22} , while W_{22}^r are the rest r columns of T_{22} , let also V_{22} be the first $k-r$ columns of T_{22}^{-1} , while V_{22}^r are the rest r columns of T_{22}^{-1} . Now, the projectors can be obtained as follows

$$\begin{aligned}W &= \begin{pmatrix} I_{n-k} & 0_{n-k, k-r} \\ 0_{k-r, n-k} & W_{22} \end{pmatrix} & W_r &= \begin{pmatrix} 0_{n-k, r} \\ W_{22}^r \end{pmatrix} \\ V &= \begin{pmatrix} I_{n-k} & 0_{n-k, k-r} \\ 0_{k-r, n-k} & V_{22} \end{pmatrix} & V_r &= \begin{pmatrix} 0_{n-k, r} \\ V_{22}^r \end{pmatrix}\end{aligned}\quad (8)$$

B. Computing a transformation for networks with monotone dynamics

It is assumed that the dynamics of the biochemical network models we are interested in can be captured via a stoichiometric matrix $S \in \mathbb{R}^{n \times m}$ and flux vector $f(x) \in \mathbb{R}^{m \times 1}$, where n is the number of species, m the number of reactions that take place and x the vector of species concentrations. The uncontrolled system then takes the form $\dot{x} = S f(x)$. We limit our focus to systems with cooperative or monotone with respect to the positive orthant $\mathbb{R}_{\geq 0}^n$ dynamics. This means that the stoichiometry matrix S and the fluxes $f(x)$ form a *cooperative* dynamical system. The following definitions make the preceding comments precise.

Definition 1: Consider the dynamical system $\dot{x} = r(x)$ where r is locally Lipschitz, $r : \mathbb{R}_{\geq 0}^n \rightarrow \mathbb{R}^n$ and $r(0) = 0$. The associated flow map is $\rho : \mathbb{R}_{\geq 0} \times \mathbb{R}_{\geq 0}^n \rightarrow \mathbb{R}^n$. The system is said to be monotone (w.r.t. $\mathbb{R}_{\geq 0}^n$) if $x \leq y \Rightarrow \rho(t, x) \leq \rho(t, y)$ for all $t \in \mathbb{R}_{\geq 0}$.

Definition 2: A matrix $M \in \mathbb{R}^{n \times n} = \{m_{ij}\}$ is said to be Metzler if $m_{ij} \geq 0$ for all $i \neq j$.

The following proposition is a simplified reformulation of a known result (cf. [13]), which establishes a straightforward test for cooperativity:

Proposition 1: A system $\dot{x} = r(x)$ is monotone with respect to the positive orthant if and only if

$$\frac{\partial(r^i(x))}{\partial x_j} \geq 0 \quad \forall i \neq j \forall x$$

Or simply put, the Jacobian of $r(x)$ is a Metzler matrix for all x in $\mathbb{R}_{\geq 0}^n$.

A generalisation can be defined with respect to any orthant by mapping this orthant onto the positive one by a linear transformation $P : \mathbb{R}^n \rightarrow \mathbb{R}^n$, where $P = \text{diag}((-1)^{\varepsilon_1}, \dots, (-1)^{\varepsilon_n})$ for some ε_i .

Hence, after linearisation around a steady-state we have system (3) with additional constraint that the drift matrix A is Metzler. We do not require B and C to be nonnegative matrices.

In this setting our model reduction problem is formulated as replacing the states x_2 with a single state, while preserving stability and the Metzler property of the drift matrix. In order to obtain the reduced order model, the generalised Lyapunov equations with block-diagonal Gramians are employed. Hence the first task is to ensure the existence of such generalised Gramians.

Lemma 1: Consider the system (3) with an asymptotically stable, Metzler drift matrix. Let the system (3) be partitioned as in (4). Let P, Q be generalised Gramians satisfying the Lyapunov inequalities (5). Then there always exist diagonal nonnegative and nonnegative semidefinite matrices P and Q satisfying (5). Consequently, there exist P and Q satisfying the partitioning as in (6).

The proof is found in appendix. Given these properties we are ready to produce a model reduction algorithm:

Reduction Algorithm:

- 1) Solve (5) and obtain the matrices P and Q with the structure described by (6).
- 2) Compute a balancing transformation T_{22} for matrices P_{22} and Q_{22} as in (7).
- 3) Define the projectors W and V as in (8) for r equal to one, let $w = W_{22}$ and $v = V_{22}$.
- 4) Compute the matrices of the truncated reduced order model as follows

$$A_t = V^T A W, \quad B_t = V^T B, \quad C_t = C W.$$

The exact expression for matrices A_t, B_t and C_t are

$$\begin{aligned} A_t &= \begin{pmatrix} A_{11} & A_{12}w \\ v^T A_{21} & v^T A_{22}w \end{pmatrix} \\ B_t &= \begin{pmatrix} B_1 \\ v^T B_2 \end{pmatrix} \quad C_t^T = \begin{pmatrix} C_1^T \\ w^T C_2^T \end{pmatrix}. \end{aligned} \quad (9)$$

Lemma 2: Let P and Q be block-diagonal matrices satisfying the conditions of Lemma 1. Assume the matrix $P_{22}Q_{22}$ is irreducible. Let T_{22} be a transformation such that $T_{22}^{-1}P_{22}T_{22}^{-T} = T_{22}^T Q_{22} T_{22} = \Sigma$, where Σ is diagonal and $\Sigma_{11} \geq \Sigma_{22} \geq \dots \geq \Sigma_{kk}$. Let w be the first column of T and v be the first column of T_{22}^{-T} . There exist such a balancing transformation T_{22} that

- 1) The vectors w and v are nonnegative.
- 2) The matrix A_t from (9) is stable and Metzler.
- 3) Let G be the full order model with a state-space realisation A, B, C and G_r be the reduced order model with a state-space realisation A_t, B_t, C_t defined in (9). Then $\|G - G_r\|_\infty \leq 2 \sum_{i=2}^k \Sigma_{ii}$.

Proof: See appendix. ■

C. Approximation Procedures

The idea of using generalised structured Gramians for structured reduction is not new (cf. [8]). In the context of biochemical networks for systems with monotone dynamics block diagonal Gramians always exist (as was just shown). Moreover, there are biochemical networks, which are not monotone, but block-diagonal Gramians still exist. Indeed it is believed that many biochemical reaction networks which do not possess the monotonicity property are actually *near monotone* [14]. In Section III-B we show that a model of yeast glycolysis is not monotone, but admits a diagonal Gramian.

Define the transformed variable as $z = Tx$ and denote by z_r be the species to be removed from the model, and z_m the states of the reduced order model. Now the equations approximating the full order dynamics can be computed as follows:

$$\begin{aligned} \dot{z}_m &= V^T f(Wz_m + W_r z_r, u) \\ \dot{z}_r &= V_r^T f(Wz_m + W_r z_r, u) = 0 \\ y_r^d &= \Omega C(Wz_m + W_r z_r) \end{aligned} \quad (10)$$

Computing the root z_r satisfying the algebraic-differential equation can be a computationally expensive task. Therefore, we also propose a truncation method, where we assume that the system is near the steady-state z_r^0 :

$$\begin{aligned} \dot{z}_m &= V^T f(Wz_m + W_r z_r^0, u) \\ y_r^d &= C(Wz_m + W_r z_r^0) \end{aligned} \quad (11)$$

For future reference we will refer to (10) as the *reduction method* and (11) as the *truncation method*.

Observe that preservation of the (global) monotonicity of the reduced nonlinear system is probably not possible in general using static space-space transformations. Consider the dynamics of z_m in (10) with $u = 0$. Let $\Gamma = Wz_m + W_r z_r$. By assumption we have that f is monotonic. In order for the unforced system in (10) to be monotonic it needs to be shown that the Jacobian of $\dot{z}_m = V_{22}^T f_1(\Gamma, 0)$ given by

$$\frac{\partial V_{22}^T f_1^i(\Gamma(z_m), 0)}{\partial (z_m)_j} \geq 0 \quad \forall i \neq j \text{ and } \forall z_m \quad (12)$$

where the vector field f is partitioned into $[f_1^T, f_2^T]^T$ conformally with $[z_m^T, z_r^T]^T$. Even for the simple case of $k-r = 1$ where V_{22} is simply the first column of T_{22}^{-1} it is difficult to determine the underlying assumptions one would need to impose on f to ensure (12) is satisfied.

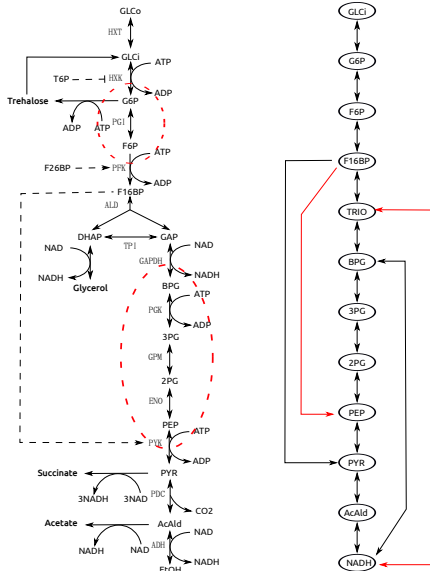


Fig. 2. The yeast glycolysis kinetic model. In the left panel the biochemical graph, and in the right panel a graph of dynamic interactions between metabolites are depicted. If the red connections are removed the dynamics of the network would become monotone.

TABLE II

DETERMINISTIC REDUCTION OF THE GLYCOLYSIS MODEL. THE ERROR OF THE OUTPUT IS GIVEN IN DIFFERENT NORMS.

II-1. QSSA

States \ Error	L_1	L_2	L_∞	$t(s)$
F6P, 2PG, PEP	1.21	0.75	0.98	163
G6P, F6P, 3PG, 2PG, PEP	2.05	1.16	1.59	214

TABLE II-2. REDUCTION BY $\{k_1, k_2\}$ STATES IN EVERY REGION

Lumped Region(s)	$\{k_1, k_2\}$	L_1	L_2	L_∞	$t(s)$
{G6P, F6P}, {2PG-PEP}	{1, 2}	1.18	0.79	1.03	161
{GLCi-F6P}, {BPG-PEP}	{2, 3}	1.05	0.57	0.78	260
{GLCi-F6P}, {3PG-PEP}	{2, 1}	0.47	0.3	0.4	137
{GLCi-F6P}, {3PG-PEP}	{1, 1}	0.14	0.07	0.09	116

TABLE II-3. TRUNCATION BY $\{k_1, k_2\}$ STATES IN EVERY REGION

Lumped Region(s)	$\{k_1, k_2\}$	L_1	L_2	L_∞	$t(s)$
{G6P, F6P}, {2PG-PEP}	{1, 2}	15.1	3.2	6.1	14
{GLCi-F6P}, {BPG-PEP}	{2, 3}	5.9	2.8	2.9	14
{GLCi-F6P}, {3PG-PEP}	{2, 1}	4.1	1.9	1.9	14
{GLCi-F6P}, {3PG-PEP}	{1, 1}	4.0	1.8	1.6	15

Using this intuition, it was not a great surprise that a linearised model around a steady-state would have block-diagonal Gramians with a sparsity pattern according to some state partitioning. However, the existence of diagonal Gramians was surprising. This meant that without any reservation we could approximate any group of states, while preserving the other states intact.

The simulation results are presented in Table II for various reduction configurations. We apply QSSA to metabolite concentrations, while using the proposed

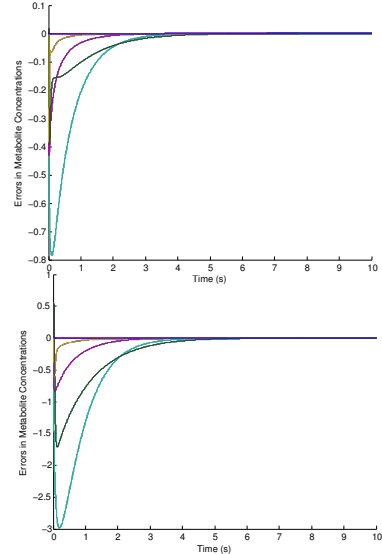


Fig. 3. (Top) The errors between the Method 1 reduced and the full order models. (Bottom) The error between the Method 2 reduced and the full order models are depicted. Blue line is the concentration of F16P metabolite, green is TRIO, red - PYR, cyan - AcAld, purple - NADH. For the methods 1 and 2 we considered the regions {GLCi-F6P}, {BPG-PEP} together and reduced two and three states, correspondingly in each region.

methods we try to lump those metabolites into one new state, so that the number of reduced states is similar in both cases. The simulation time in seconds is denoted as t . First two rows of each subtable in Table II can be compared directly, and it is clear that the reduction method performs better in terms of quality than QSSA.

The proposed reduction method is also more flexible in terms of reduction choices. In the third row of Subtable II-2, the region {3PG-PEP} contains three metabolites; however, we reduced only two states after computing the state-space transformation. In the fourth row, additionally to reducing only one state in region {3PG-PEP}, in the region {GLCi-F6P} we reduce only one state. This provides us with the best model among all the reduction attempts.

The results of the truncation method (Table II-2) may seem unattractive due to lower approximation quality; however, the difference in terms of qualitative behaviour of the full and the truncated reduced models is not as substantial as the numbers suggest. This is illustrated in Figure 3. The simulation time of the truncated reduced order model is lower by an order of magnitude in comparison with QSSA and the reduction method.

IV. CONCLUSION

We have presented a method for obtaining structured reduced order models of biochemical reaction networks. The algorithm involves computation of a state-space

transformation around a steady-state, followed by a truncation and/or lumping procedure which preserves structure and local monotonicity and stability of the system. The algorithm was illustrated on two numerical examples, one of which was not monotone and compared with a *standard* QSSA based reduction.

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APPENDIX

Proof of Lemma 1. It suffices to show that there exist a *strictly* diagonal P satisfying the controllability Lyapunov inequality. Similar arguments hold for a diagonal Q with satisfying the observability Lyapunov inequality. It is known that there exist a diagonal P satisfying the following inequality $AP + PA^T \leq -\delta I$ for a positive δ , given an asymptotically stable matrix A . Let $X = AP + PA^T$. Set $\gamma = \bar{\sigma}(BB^T)/\delta$, clearly γ is such that $\gamma X + BB^T$ is a negative semidefinite matrix. Therefore exist a diagonal P satisfying the Lyapunov inequality, which completes the proof.

Proof of Lemma 2. 1) The existence of a balancing transformation is an established result (cf. [18]). $P_{22}Q_{22}$ is an irreducible matrix with nonnegative entries, therefore by Perron-Frobenius theorem there exist a positive eigenvector w such that $P_{22}Q_{22}w = \Sigma_{11}^2 w$ where Σ_{11}^2 is the entry $(1, 1)$ of the matrix Σ^2 and the largest eigenvalue of $P_{22}Q_{22}$. From the existence of T , it follows that $T\Sigma^2T^{-1} = P_{22}Q_{22}$, where Σ^2 is a diagonal matrix. Hence T contains right eigenvectors to a matrix $P_{22}Q_{22}$ and without loss of generality w is the first column of T . Similarly it can be shown that v the first column of T^{-T} is nonnegative.

2) Stability of the matrix A_t is a collection of known results, but it is presented for completeness. Let T be $\text{diag}(I_{n-k}, T_{22})$. Introduce the following partitioning of these matrices:

$$T^{-1}AT = \begin{pmatrix} A_t & A_{tr} \\ A_{rt} & A_{rr} \end{pmatrix} \quad T^{-1}PT^{-1} = \begin{pmatrix} \tilde{P} & 0 \\ 0 & \tilde{\Sigma} \end{pmatrix}$$

$$\tilde{P} = \begin{pmatrix} P_{11} & 0 \\ 0 & \Sigma_{11} \end{pmatrix} \quad \tilde{\Sigma} = \text{diag}(\Sigma_{22}, \Sigma_{nn})$$

Now stability of A_t can be established by simply writing the Lyapunov inequalities in the new variables.

$$T^{-1}ATT^{-1}PT^{-T} + T^{-1}PT^{-T}T'A'T' \leq 0$$

$$\begin{pmatrix} A_t & A_{tr} \\ A_{rt} & A_{rr} \end{pmatrix} \begin{pmatrix} \tilde{P} & 0 \\ 0 & \tilde{\Sigma} \end{pmatrix} + \begin{pmatrix} \tilde{P} & 0 \\ 0 & \tilde{\Sigma} \end{pmatrix} \begin{pmatrix} A_t' & A_{tr}' \\ A_{rt}' & A_{rr}' \end{pmatrix} \leq 0$$

$$\begin{pmatrix} A_t\tilde{P} + \tilde{P}A_t' & A_{tr}\tilde{\Sigma} + \tilde{P}A_{tr}' \\ * & A_{rr}\tilde{\Sigma} + \tilde{\Sigma}A_{rr}' \end{pmatrix} \leq 0$$

Proving that A_t is Metzler is also straightforward. $A_{12}w$ $v'A_{21}$ are nonnegative since w, v, A_{12}, A_{21} are individually nonnegative [19]. All is left to show that $v'A_{22}w$ is a negative scalar. Since $A_t\tilde{P} + \tilde{P}A_t' \leq 0$ then

$$\begin{pmatrix} A_{11}P_{11} + P_{11}A_{11}' & A_{12}w\Sigma_{11} + P_{11}A_{21}'v \\ * & v'A_{22}w\Sigma_{11} + \Sigma_{11}w'A_{22}'v \end{pmatrix} \leq 0$$

and hence $v'A_{22}w\Sigma_{11} + \Sigma_{11}w'A_{22}'v < 0$. This implies that $v'A_{22}w$ is negative since $\Sigma_{11} > 0$.

3) This result is shown in [8].