



Model reduction in chemical dynamics: slow invariant manifolds, singular perturbations, thermodynamic estimates, and analysis of reaction graph

AN Gorban^{1,2}

The paper has two goals:

- (1) It presents basic ideas, notions, and methods for reduction of reaction kinetics models: quasi-steady-state, quasi-equilibrium, slow invariant manifolds, and limiting steps.
- (2) It describes briefly the current state of the art and some latest achievements in the broad area of model reduction in chemical and biochemical kinetics, including new results in methods of invariant manifolds, computation singular perturbation, bottleneck methods, asymptotology, tropical equilibration, and reaction mechanism skeletonization.

Addresses

¹ Department of Mathematics, University of Leicester, Leicester LE1 7RH, UK

² Lobachevsky University, Nizhni Novgorod, Russia

Corresponding author: Gorban, AN (a.n.gorban@le.ac.uk)

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methods were developed together with the first theories of complex chemical reactions. Three simple basic ideas have been invented:

- The *Quasi-Equilibrium* approximation or QE (a fraction of reactions approach their equilibrium fast enough and, after that, remain almost equilibrated).
- The *Quasi Steady State* approximation or QSS (some of species, very often these are some of intermediates or radicals, exist in relatively small amounts; they reach quickly their QSS concentrations, and then follow, as a slave, the dynamics of these other species remaining close to the QSS). The QSS is defined as the steady state under condition that the concentrations of other species do not change.
- The *limiting steps* or bottleneck is a relatively small part of the reaction network, in the simplest cases it is a single reaction, which rate is a good approximation to the reaction rate of the whole network.

Introduction

Three eras (or waves) of chemical dynamics can be associated with their leaders [1]: the van't Hoff wave (the first Nobel Prize in Chemistry, 1901), the Semenov–Hinshelwood wave, and the Aris wave. The problem of modelling of *complex reaction networks* was in the focus of chemical dynamics research since the invention of the concept of ‘chain reactions’ by Semenov and Hinshelwood (the shared Nobel Prize in Chemistry, 1956). Aris’ activity was concentrated on the detailed systematization of mathematical ideas and approaches for the needs of chemical engineering. In the engineering context, the problem of modelling of complex reactions became even more important.

A mathematical model is an intellectual device that works [2]. Creation of such working models is impossible without the well developed technology of model reduction. Therefore, it is not surprising that the model reduction

More precise formal discussion is presented in the following sections.

In 1980s–1990s the model reduction technology was enriched by several ideas. Most important of them are: the Method of Invariant Manifolds (MIM) theory and algorithms [3[•],4[•]], the special Intrinsic Low Dimensional Manifold (ILDM) method for approximation of slow motion [5[•]], the Computational Singular Perturbation (CSP) method for the iterative approximation of both slow and fast motions [6[•]], and the sensitivity analysis of complex kinetic systems [7[•]].

Development of lumping analysis was important for general understanding of model reduction in chemical kinetics [8[•]]. The lumped species is considered as a linear combination of the original ones. These combinations are often guessed on the basis of known kinetic properties and can be improved by iterative methods and observer

theory. The standard examples are: the lumped species are identified as the sums of species in selected groups (a very popular approach with many practical applications, e. g., [9]); the lumped species are the numbers of links and structural fragments of various types and in different states (this approach has many applications, from petrochemistry [10] and modelling of intracellular networks [11] to the Internet dynamics [12[•]]).

The main achievements of this period (1980s–1990s) in model reduction were summarized in several books and surveys [13,14,15[•],16].

The technological elaboration of these ideas and assimilation of those by the modelling practice took almost thirty years. Much efforts have been invested into computational improvements and testing with the systems of various complexity. Some new ideas were proposed and developed.

The QE, QSS, MIM, and CSP methods can be applied to any differential equation with explicit or implicit (hidden) separation of time. They use the structure of reaction network as a tool for creation of kinetic equations. In the classical methods, only the limiting step approach (the bottleneck method) works directly with the reaction graph. Recently, the model reduction methods which use the structure of the reaction network, were developed far enough and attract many different techniques, from sensitivity analysis to algebraic geometry and tropical mathematics.

The first step in the next section is a ‘step backwards’, a brief introduction of the classical methods. Then we move to modern development.

QE, QSS, MIM and CSP in ODE framework

Formally, the standard models of chemical kinetics are systems of Ordinary Differential Equations (ODE). The general framework looks as follows. Let U be a bounded domain in R^n . Assume that vector fields $F_{\text{fast}}(x)$ and $F_{\text{slow}}(x)$ are defined and differentiable in a vicinity of \bar{U} (in real applications these vector fields are usually analytical, or even polynomial or rational). Let U be positively invariant with respect to $F_{\text{fast}}(x)$ and $F_{\text{slow}}(x)$. Consider dynamical system with the explicit *fast–slow time separation*:

$$\frac{dx}{dt} = F_{\text{slow}}(x) + \frac{1}{\varepsilon} F_{\text{fast}}(x), \quad (1)$$

where $\varepsilon > 0$ is a small parameter. The *fast subsystem* is

$$\frac{dx}{d\tau} = F_{\text{fast}}(x). \quad (2)$$

Here, time τ is used to stress that this is the ‘fast time’, $\tau = t/\varepsilon$. If the fast system (1) converges to an

asymptotically stable fixed point in U and has no fixed points on the border of U then for sufficiently small ε the slow vector field becomes practically invisible in the dynamics of (1), that is there is no slow dynamics.

Let the fast system (2) be neither globally stable nor ergodic in U . Assume that it has the conservation laws $b_i(x)$ ($i = 1, \dots, k$) and for each $x_0 \in U$ the fast system on the set $b_i(x) = b_i(x_0)$ converges to a unique stable fixed point $x^*(b)$, where b is the vector of values $b_i(x)$. Then the slow system describes dynamics of conservation laws b :

$$\frac{db}{dt} = Db_{x=x^*(b)}[F_{\text{slow}}(x^*(b))], \quad (3)$$

where $Db_{x=x^*(b)}$ is differential of $b(x)$ at the point $x^*(b)$. For linear conservation laws $Db = b$ and the slow equations have the simple form

$$\frac{db}{dt} = b[F_{\text{slow}}(x^*(b))]. \quad (4)$$

The QE manifold is parametrized by the conservation laws with functions $x^*(b)$. It should be stressed that the slow equations in their natural form (3) and (4) describe the dynamics of the conservation laws b and not the dynamics of the selected ‘slow coordinates’. The problem of projection onto slow manifold is widely discussed [17[•],18,19[•]]. According to the Tikhonov theorem, dynamics of the general system (1) from an initial state x_0 under the given assumptions can be split in two stages: fast convergence to the QE manifold $x^*(b)$ (the *initial layer*, convergence to a small vicinity of $x^*(x_0)$), and then slow motion in a small vicinity of the QE manifolds.

The QE assumption is the separation of reactions onto slow and fast: F_{slow} includes all the terms from the slow reactions, F_{fast} includes all the terms from the fast reactions and the slow manifold $x^*(b)$ consists of *equilibria* of the fast reactions parametrized by the conservation laws. The ‘thermodynamic’ behaviour of fast reactions (convergence to equilibrium, which is unique for any given values of the conservation laws) is essential to application of the Tikhonov theorem. Slow reactions can be extended by including external fluxes, they do not change the asymptotic form (3) and (4).

Combining of fast subsystems from the fast reactions is so popular [20] that a special warning is needed: there exists another widely used approximation without separation of reactions into fast and slow (see QSS below).

It should be stressed that the physical and chemical nature of the convergence to equilibrium of fast reactions may vary. It may follow from thermodynamic conditions like principle of detailed balance or semi-detailed balance. It may have also completely algebraic nature. For

example, any linear (monomolecular or pseudomonomolecular) system tends to a fixed point, which is unique for any given values of conserved quantities. The mass action law systems with reactions ‘without interaction of different substances’ $\alpha_r A_i \rightarrow \sum_j \beta_{rj} A_j$ provide us with another example [21] (here A_i are the components, r is the number of reaction, and the coefficients are non-negative integers).

The QSS approximation does not separate the reactions into slow and fast. Usual application of the QSS is the slaving dynamics of the active intermediates in combustion (Semenov) or in catalysis (Hinshelwood). The stable reagents participate in the same reactions as the intermediates do and, therefore, we cannot consider them as ‘slow’ reagents. The nature of small parameter in this case is very different [22]. It is the smallness of the *amount* of intermediates. Let us illustrate this small parameter for heterogeneous catalytic reactions [23]. We use notations: V is the volume of reactor, S is the surface of catalyst, N_g is the vector of amounts of the gas components, N_s is the vector of amounts of the surface components, $c_g = N_g/V$, $c_s = N_s/S$. Let us measure V and S in moles (i.e. we use PV/RT for some average values of the pressure P and temperature T instead of V and the number of moles of active centres on the surface instead of S) for creation of dimensionless variables. The kinetic equations are:

$$\frac{dN_g}{dt} = SF_g(c_g, c_s), \quad \frac{dN_s}{dt} = SF_s(c_g, c_s),$$

where F_g and F_s are combined from the reaction rate per unit surface (mole of active centres). Notice that usually in the selected units $S \ll V$ (if the pressure is not extremely low). Under given V , we can write equations with a small parameter $\varepsilon = \frac{S}{V}$.

$$\frac{dc_g}{dt} = \varepsilon F_g(c_g, c_s), \quad \frac{dc_s}{dt} = F_s(c_g, c_s).$$

After the change to the slow timescale, $\theta = \frac{S}{V}t$ we get the slow and fast subsystems:

$$\dot{c}_g = F_g(c_g, c_s); \quad \dot{c}_s = \frac{1}{\varepsilon} F_s(c_g, c_s). \quad (5)$$

If the fast dynamics of c_s tends to the asymptotically stable fixed point (quasi-steady-state) $c_s^*(c_g)$ for any fixed value of c_g then we return to the previously described situation: the motion can be separated into two steps: first, c_s goes fast into a small vicinity of $c_s^*(c_g)$ (initial layer) and then c_g slowly changes in vicinity of this manifold.

In the QSS approximation, the smallness of amount of intermediates is the crucial assumption. There may be

various explanation of this smallness. For example, in catalysis this is the smallness of the amount of the catalyst. In combustion, the high activity of the intermediates leads to their short life time.

The list of variables for QSS exclusion can change in time. The smallness of concentration can serve as a criterion for the extension/reduction of this list [19*]. The ‘speed coefficients’ were introduced recently [24] for ranking variables according to how quickly they approach their momentary steady-state. These coefficients are used for a straightforward choice of variables for QSS elimination, while preserving dynamic characteristics of the system.

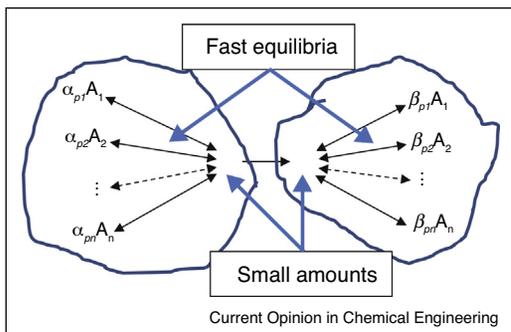
In addition to the different nature of small parameters, the QSS differs from the QE in one more essential aspect: for the QE, the fast system is just chemical kinetics of the set of fast reactions. It has all the thermodynamic properties expected for the chemical kinetics equations, like positivity of entropy production. It cannot have bifurcations, oscillations, etc. The slow system in the QE approximation also has the thermodynamic properties. This is a particular case of the general theorem about the *preservation of the type of dynamics*: the QE approximation and the fast subsystem inherit thermodynamic behaviour from the original system [25]. This property makes QE a promising initial approximation for various iterative model reduction procedures [25].

In the QSS, the fast system can have many steady states, oscillation, etc. These critical effects in the QSS approach are considered as the symptoms of physical critical effects, for example ignition: the original system with thermodynamic behaviour has no bifurcations but just high sensitivity, at the same time the fast system in the QSS approximation has bifurcations.

If the fast system does not converge to equilibrium then the methods of *averaging* can work [26]. Instead of partial equilibria or quasi-steady-states the so-called ‘ergodes’ are used (subsets, on which the fast systems are ergodic).

All the methods of invariant manifold in chemical kinetics were introduced for generalization and improvement of the QE and QSS. The earliest prototype was the Chapman–Enskog method in the kinetic foundation of fluid dynamics but this method used the Taylor series expansion in powers of a small parameter. The second approximation from this series is already singular. The iterative MIM was developed for the Boltzmann equations for correcting these singular properties of the Chapman–Enskog expansion [4*, 27**] and for solution of Hilbert’s 6th Problem [28]. The mathematically rigorous version of the Chapman–Enskog method for finite-dimensional ODEs was developed by Fenichel [29] and was used as the prototype in many later works (see the collection of papers [30]).

Figure 1



The Michaelis–Menten–Stueckelberg limit: intermediates B are in fast equilibrium with reagents A_i and are present in small amount (QSS). This limit results in mass action law for the brutto reactions between A_i .

Combination of the QE and QSS assumptions (fast partial equilibria and small amounts of intermediates, for example) leads to important general results. It was used in 1913 by Michaelis and Menten. They proved that under this assumption the intermediates could be completely excluded from kinetic equations and the resulting kinetics will obey mass action law again. In 1952, Stueckelberg used this QE+QSS combination for proving the semi-detailed balance condition for Boltzmann's equations (later, this condition was rediscovered and popularized as the *complex balance* condition). The detailed review was presented and the general Michaelis–Menten–Stueckelberg asymptotic theorem was formulated and proved in [31*,32] (see Figure 1).

If there exist no fast equilibria (no QE), then the QSS approximation alone does not lead to the simple mass action law after exclusion of the intermediates. Nevertheless, if the mechanism of the intermediates transitions is linear then the explicit analytic expressions for the QSS reaction rates are obtained [23]. The simplest of them, for the enzyme (E)–substrate (S) reaction, $S + E \rightleftharpoons SE \rightarrow E + P$, is known as the Michaelis–Menten kinetics (produced by Briggs and Haldane in 1925).

For non-linear reactions between intermediates, they usually cannot be excluded from the equations analytically but an equation for the reaction rate can be produced. The method of *kinetic polynomial* gives the algebraic equation for the reaction rate [33*]. This equation (the kinetic polynomial) is produced by the exclusion methods (the constructive algebraic geometry) and is successfully used in analysis of catalytic reactions.

The MIM aims to find the slow invariant manifold (Figure 2) [3*,4*,34,19*]. Invariance has simple definitions, both analytic and geometric ones. Consider a

system of ODE, $\dot{x} = F(x)$. Imagine that we found such a (nonlinear) coordinate transformation after that the vector x is represented as a direct sum $x = y \oplus z$ and the equations have the form

$$\dot{y} = F_y(y, z), \quad \dot{z} = F_z(y, z), \quad (6)$$

where $F_y(0, z) = 0$. This means that if $y(0) = 0$ then $y(t) = 0$ for solutions of the system.

The manifold $y = 0$ is invariant with respect to the system. Of course, it is not necessary to assume a global transformation with this property. We can use local transformations under condition that they define the same manifolds $y = 0$ in intersections (to provide gluing of the local pieces). The definition of slowness is much more sophisticated. It can be done rigorously for systems with existing slow parameters ε using analytical continuations from the very small values of ε or from a vicinity of an attractor (e.g. a stable fixed point) using separation of the relaxation modes into fast and slow ones (e.g. separation of the invariant subspaces of Jacobian by real parts of eigenvalues) [27**].

Far from these continuations, there exist two popular heuristics: one used the eigenspaces of Jacobians in various states [16], another relies on a special iteration procedures (a special version of the Newton–Krylov method) [13]. Both approaches converge to a slow manifold for sufficiently small ε or in a vicinity of an asymptotically stable equilibrium under some simple technical conditions (see [13,35,36*]).

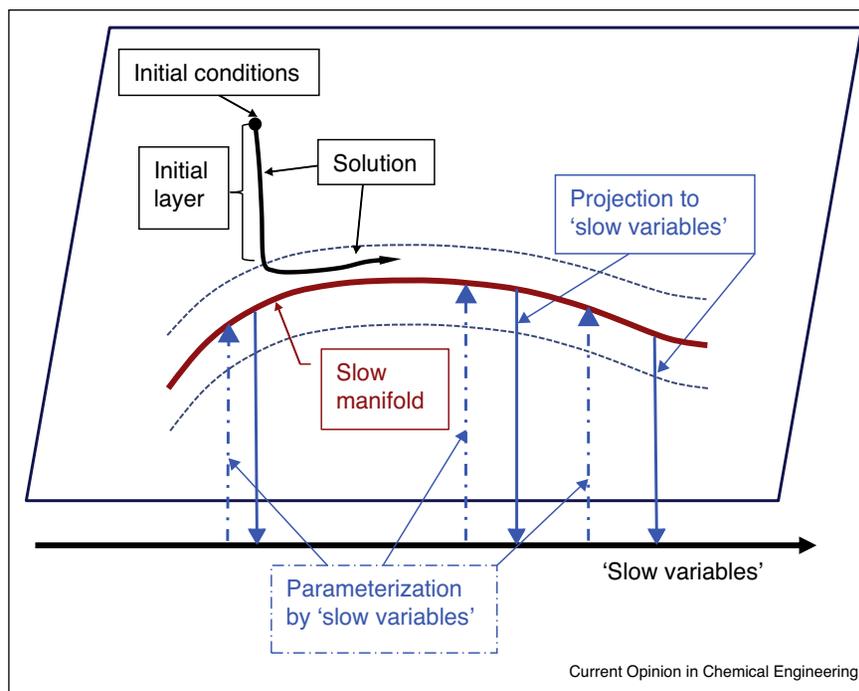
A special model reduction method, which utilized the analytic continuation from a vicinity of a fixed point and Lyapunov auxiliary theorem was developed [37].

The CSP looks for more than just a slow manifold. It tries to find the complete slow-fast decomposition, that is to transform the initial system of ODE $\dot{x} = F(x)$ into a decoupled form

$$\dot{y} = F_y(y), \quad \dot{z} = F_z(z), \quad (7)$$

where the non-diagonal terms (dependence of \dot{y} on z and \dot{z} on y) vanish. Of course, this complete decomposition could be rarely found explicitly (as well as the slow invariant manifold) but the CSP tends to decrease the non-diagonal terms iteratively. Again, the definition of decomposition is simple and straightforward, but the attribution of slow/fast properties may be complicated and can be done rigorously for families of systems with a small parameter or near a stable attractor. Relations between QE, QSS, and CSP were analysed in a series of works [38,39]. The classical heuristic for the slow-fast

Figure 2



Slow invariant manifold.

CSP decomposition used the eigenvectors and eigenspaces of the Jacobians at all states but very recently one of the inventors of the CSP proposed a direct iteration method, which can lead to the same result avoiding expensive calculations of the eigenvalues and eigenvectors in transient states [40^{••}].

During the last decade much work was done to improve the computational efficiency and extend the area of applicability of the MIM and CSP. In particular, a grid-based computational method for slow invariant manifolds was elaborated [41].

The method of Reaction–Diffusion Manifolds (REDIM) [42,43[•],44] was developed to extend the MIM for handling the diffusion processes in combustion problems [43[•]]. It represents a modification of the Film Equation [13,14] and of functional iteration technique [3[•]] to approximate a slow invariant manifold for a reaction–diffusion system. Recently, the REDIM method was improved to be able to generate and to approximate a slow manifold of arbitrary dimension by employing its hierarchical structure [43[•]]. The REDIM was applied for model reduction in various combustion systems.

The CSP was generalized and implemented as a part of a general strategy for analysis and reduction of uncertain chemical kinetic models [45[•]].

Lumping analysis was reformulated as a particular case of MIM [46] and computational possibilities of this approach were tested. The reaction rate constants are usually defined with uncertainty. A Bayesian automated method was implemented for robust lumping for systems with parameter variability [47]. The method works stepwise, reducing the system's dimension by one at each step.

The theory and methods of invariant manifolds are used for modern development of the theory of critical simplification. In 1944, Lev Landau noticed that near the loss of stability the amplitude of the emergent 'principal motion' satisfies a very simple equation. It is an example of the 'bifurcational parametric simplification'. In chemical kinetics, the concept of 'critical' simplification was proposed in chemical kinetics by Yablonsky and Lazman for the oxidation of carbon monoxide over a platinum catalyst using a Langmuir–Hinshelwood mechanism (see [33[•]]). The main observation was a simplification of the mechanism at ignition and extinction points. This is a very general phenomenon known for various bifurcations. For the equations of chemical kinetics, the theory of critical simplification was developed recently [48[•]] using the constructive theory of invariant manifolds.

Various methods of construction of slow invariant manifolds were tested and compared using a simple example

[49^{*}]. Method of invariant grids [41] was employed in this work for iteratively solving the invariance equation. Various initial approximations for the grid are considered such as QE, Spectral QE, ILDM and Symmetric Entropic ILDM (proposed earlier [19^{*}]). Slow invariant manifold was also computed using CSP method. A comparison between method of invariant grids and CSP is also reported. Although CSP and the tested MIM are based on completely different construction of iterations, the comparison shows very similar results in terms of accuracy of slow invariant manifold description.

Thermodynamics gives a convenient opportunity to formulate the QE assumption. If the fast reactions obey thermodynamics then the corresponding thermodynamic potential is a Lyapunov function: it should change monotonically along the fast motion [23,13,50,51], and QE can be described as a conditional extremum (i.e. maximum for entropies and free entropies or minimum for free energies) of the thermodynamics potential. In this formalism the reactions are not needed, only the plane of fast motion is necessary. This simple idea [19^{*}] gave rise to many ‘constrained equilibria’ approximations [52^{*},53^{*}]. For example, a new version of the QE was proposed, the spectral QE manifold, that consists of partial equilibria in the planes of fast motions, which are parallel to fast eigenspaces of Jacobian at equilibrium [54].

Thermodynamics was used for comparing all reversible reactions by the same measure: entropy production. It was proposed to exclude almost equilibrated reversible reactions from the reaction mechanism [55]. The distance from the reaction equilibrium was measured by entropy production. The total entropy production should not change significantly in this procedure. (If we assume the detailed balance, then the entropy produced by a reversible reaction measures how far is it from equilibrium.) This method was used for defining of the compartments in the composition space with the different reaction mechanism for hydrogen combustion [56].

Recently, this method was re-engineered and applied to auto-ignition of n-heptane with extraction of two skeletal mechanisms, and for analysis of spatially varying premixed laminar flames [57^{*}]. For partially irreversible reactions, there exist special Lyapunov functions as well [58^{*}].

The fast–slow separation in the form (5) may be hidden and should be revealed. Let us look on the system with fast–slow separation (Figure 2). Two domains can be distinguished there: the domain where the system change is slow and the domain where the change is relatively fast. Moreover, the fast area is expected to be larger (the system ‘shrinks’ to the smaller-dimensional manifold of slow motions). This heuristic idea gave rise to development of a Singularly Perturbed Vector Fields (SPVF)

theory [59] and of a Global Quasi-Linearization (GQL) approach in its framework [60].

In this way, the transformation to the explicitly decomposed form (5) is constructed by a linear interpolation of the system vector field (1) from a randomized sample of vectors x [59,61^{*},62,63]. The results of application of the GQL and the QSS were systematically compared [64^{*},65].

The model reduction methods based on the randomized sampling and principal component analysis are systematically used under the name ‘Proper Orthogonal Decomposition’ (POD) [66]. The POD is an a posteriori, data dependent projection method. The data points are either given by samplings from experiments or by trajectories of the physical system extracted from simulations of the full model (the so-called ‘snapshots’). This point of view is often translated into the question: ‘Find a subspace approximating a given set of data in an optimal least-squares sense’ [67]. Various linear and non-linear versions and generalizations of the principal component analysis are applied for dimensionality reductions of snapshots [68]. In particular, a modification of the POD with preservation of some original state variables is proposed [69].

We can expect intensive development of new model reduction methods with applications of the classical and new *data mining techniques*: independent component analysis, various methods of clustering, artificial neural networks, and other machine learning methods. For example, the profile likelihood approach allows solving the model reduction problem together with the identification problem and analysis of parameter identifiability and designates likely candidates for reduction. The following references demonstrate some other recent efforts in this direction [70–75,76^{*},77].

Reaction networks, limiting steps, and dominant paths

Most of the methods described above can be applied to more general systems of ODE than reaction networks. They exploit the slow-fast separation and some of them utilize the thermodynamic Lyapunov functions (like QE [19^{*}]). More rarely, the model reduction methods employ both the thermodynamic functions and reaction mechanism, like, for example, the method for extraction of skeletal mechanisms comparing entropy production by various reversible reactions [57^{*}].

There exists a family of the model reduction methods, which intensively use the structure of reaction networks. The oldest, simplest, and, perhaps, the most used method of model reduction in chemical kinetics is the method of limiting step — or bottleneck [78].

Consider systems obeying mass action law: the reaction rate r of the reaction $\sum_i \alpha_{\rho i} A_i \rightarrow \sum_i \beta_{\rho i} A_i$ is $r_\rho = k_\rho \prod_i c_i^{\alpha_i}$, where A_i are the components, index ρ is a reaction number, $\alpha_{\rho i}$ and $\beta_{\rho i}$ are non-negative stoichiometric coefficients, k_ρ is the reaction rate constant, and c_i is the concentration of A_i . The stoichiometric vector of the reaction γ_ρ has coordinates $\gamma_{\rho i} = \beta_{\rho i} - \alpha_{\rho i}$. The kinetic equations (under constant volume) are

$$\dot{c} = \sum_{\rho} r_{\rho} \gamma_{\rho},$$

where k is the reaction number.

A chain of linear irreversible reactions with non-zero rate constants $A_1 \rightarrow A_2 \rightarrow \dots \rightarrow A_m$ has m non-zero eigenvalues of the kinetic equation matrix, which coincide with $-k_i$, where k_i ($i = 1, \dots, m-1$) is the reaction rate constant of the reaction $A_i \rightarrow A_{i+1}$. Therefore, the relaxation rate is determined by the smallest constant. In a irreversible cycle $A_1 \rightarrow A_2 \rightarrow \dots \rightarrow A_m \rightarrow A_1$ the smallest constant determines the stationary reaction rate. Indeed, in a steady state all the reaction rates in such a cycle should be equal: $k_i c_i = k_j c_j = w$. Therefore, in a steady state $c_i = w/k_j$, and $w = \sum_i c_i / \sum_j (1/k_j)$. If $0 < k_1 < \varepsilon k_i$ ($i \neq 1$) then $k_1 \sum_i c_i > w > k_1 \sum_i c_i / (1 + m\varepsilon)$. If $0 < \varepsilon \ll 1/m$ then $w \approx k_1 \sum_i c_i$. The relaxation time for an irreversible cycle with limiting step is inverse second reaction rate constant [79**]. Indeed, the simple calculations show that for sufficiently small ε the minimal non-zero eigenvalue of the kinetic matrix is close to the second constant in order.

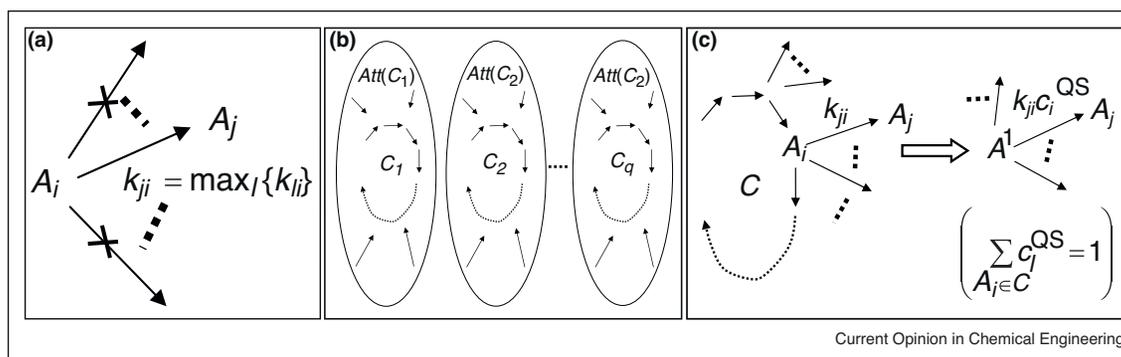
The simple and widely used idea of the limiting steps was transformed into calculation of the hierarchical dominant

paths (Figure 3) for multiscale reaction networks [79**]. Consider linear reaction network $A_i \rightarrow A_j$ with reaction rate constants k_{ji} . Assume that in each reaction 'fork' there exists a dominant reaction (Figure 3a): if $k_{ji} = \max\{k_{ij}\}$ then $k_{qj}/k_{ji} < \varepsilon$ for some small parameter ε and any $q \neq j$. Delete all the non-dominant reactions from the network. As a result, each component A_i will have only one outgoing reaction. Thus, the network is transformed into a discrete dynamical systems, where A_i are states and reactions are transitions. Every motion in such a dynamical system is attracted by a cycle or a fixed point (Figure 3b).

This is not the end of the story. Find for every cycle C the quasi stationary distribution: if we numerate the components in the cycle in the order of reactions A_1, \dots, A_k then $c_i^{\text{QS}} = \frac{1}{k_i} / \sum_j \frac{1}{k_j}$, where k_i is the reaction rate constant of the reaction $A_i \rightarrow \dots$ from the cycle. Glue cycles into new vertices with the constants of outgoing reactions multiplied by c_i^{QS} (Figure 3c). Iterate the steps a-c of the analysis. The procedure will converge in the finite number of steps. We obtain a hierarchical dominant path: first, reaction converges to cycles (or fixed points), then, slower, to cycles of cycles, etc. It is proven [79**] that the eigenvalues and eigenvectors of the initial network are well approximated by this procedure for sufficiently small ε . This approach was successfully applied to modelling the mechanisms of microRNA action [80,81*] and other biochemical reactions [82].

In order to find the dominant subsystems and paths in nonlinear reaction networks, the methods of tropical (max,+) algebras were employed [83*,84]. The notion of tropical equilibration was elaborated that provides approximate descriptions of the slow invariant manifolds. Compared to computationally expensive numerical

Figure 3



Hierarchical dominant path for linear system: (a) for each component retain the output reaction with maximal reaction rate: in each reaction 'fork' remains only dominant output and the reaction graph becomes a discrete dynamic system; (b) this discrete dynamic system converges to cycles (or fixed points); (c) cycles are glued in points, the output reactions are renormalized. A new reaction graph is constructed, where some vertices are glued. Then return to the step (a) for the new network. Iterate until all the trajectories of the discrete dynamical system converge to fixed points. This hierarchy of networks represents the hierarchical dominant path and provides us with asymptotic formulas for eigenvectors and eigenvalues of the initial network [78,82,79**].

algorithms such as the CSP, the tropical approach is symbolic. It operates by the orders of magnitude instead of precise values of the model parameters. The tropical methods provide identification of metastable regimes, defined as the low dimensional regions of the phase space close to which the dynamics is much slower compared to the rest of the phase space. These metastable regimes depend on the network topology and on the orders of magnitude of the kinetic parameters.

The local asymptotics of the algebraic curves are described by the tropical (or min-plus) systems of equations on their dominant exponents following the Newton polygon method. A necessary (tropical) condition of being a solution is the coincidence of the dominant orders of growth of at least of two monomials of the equation. These conditions provide a system of linear inequalities in the dominant exponents which one can handle by means of the known algorithms for linear programming. Thus, the problem of solving a system of algebraic equations is reduced to a combinatorial one of determining the dominant monomials. Since solving tropical systems is easier in general than solving algebraic systems, one can get a benefit in calculating asymptotics.

Extensive application of this method to biochemical network models demonstrates that the number of dynamical variables in the minimal models of large biochemical networks may be rather small and the number of metastable regimes is sub-exponential in the number of variables and equations [85]. The dynamics of the network can be described as a sequence of jumps from one metastable regime to another. A geometrically computed connectivity graph restricts the set of possible jumps. The graph theoretical symbolic preprocessing method significantly reduces computational complexity of the analysis of reaction networks and computation of parameter regions for networks multistationarity [86].

Model reduction is a necessary tool for model composition in chemistry and biochemistry of large reaction networks [87]. The model should be reduced even before its creation [19^{*}]. The full model can be imagined but its identification and reliable verification is often impossible. To obtain the model that works, we have to reduce the full model before identification. More precisely, model identification and model reduction should be combined in one process. There are several attempts of such an approach. For example, the combination of model reduction and parameter estimation based on Rao-Blackwellised particle filters decomposition methods was proposed for non-linear dynamical biochemical networks [88] and tested successfully on synthetic and experimental data.

Asymptotology [79^{**}] and tropical asymptotics [83,84] operate by the orders of smallness rather than by

computational accuracy and aim to find the limit ‘skeleton’ of the reaction mechanism (under some additional conditions like preservation of connectivity or persistence).

Simultaneously, a new technique for model reduction was developed on the basis of the idea of controllable accuracy and error propagation [89]. A geometric error propagation method creates a hierarchy of increasingly simplified kinetic schemes containing only important chemical paths. ‘Importance’ is defined using preset accuracy targets and user-defined error-tolerance. The proposed technology operates with large and very large reaction mechanisms (hundreds and thousands of reactions). The model reduction in this technology is intrinsically connected to model identification and validation procedures: model reduction is an important component of these operations.

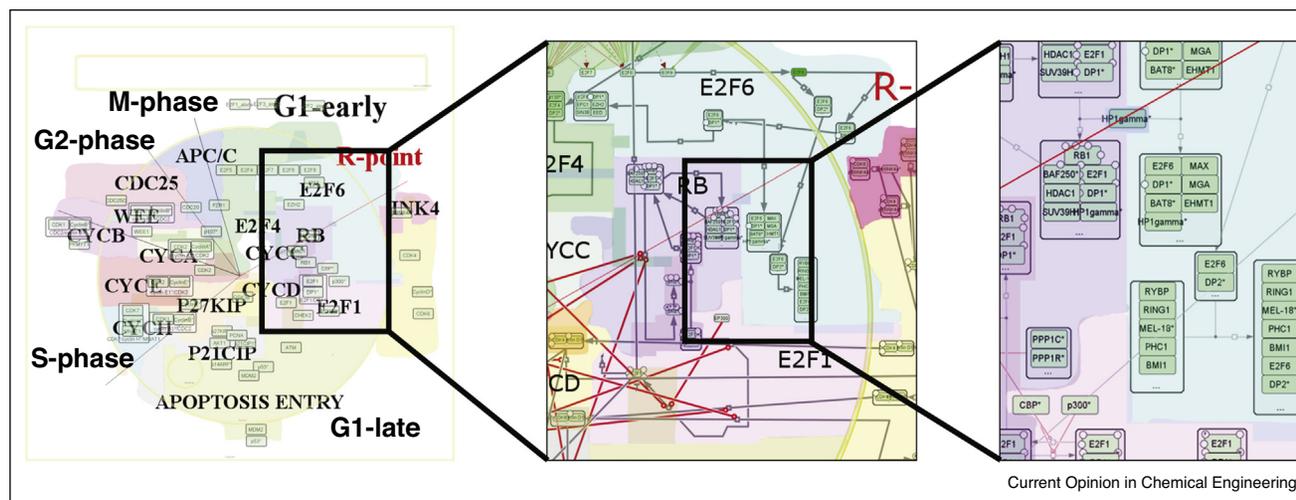
For example, the advanced Directed Relation Graph with Error Propagation and Sensitivity Analysis (DRGEP-SA) method was developed [90^{*}]. Two skeletal mechanisms for n-decane were generated by this method from a detailed reaction mechanism for n-alkanes. The detailed mechanism included 2115 species and 8157 reactions [90^{*}].

Another reaction mechanism reduction method, Simulation Error Minimization Connectivity Method (SEM-CM) produces several consistent mechanisms, which include the preselected important species [91]. It starts from the preselected important species and adds strongly connected sets of species. These strongly connected sets are identified using the Jacobian (sensitivities). This growth of the mechanism is controlled by the simulation accuracy and is terminated when the required accuracy is achieved. The method was tested on the reaction mechanism with 6874 reactions of 345 species. The reduced mechanism included 246 reactions of 47 species, and numerical simulations became two orders faster [91].

Various methods of reaction mechanism ‘surgery’ is now one of the hottest topics in reduction of large and very large models in chemical engineering [57^{*},92–95]. Surprisingly, the geometric details of this analysis seem to be very close to the geometric methods of asymptotology and tropical asymptotic.

For large and very large reaction systems, the reaction graph can be considered as an analogue of a geographic map of a large area. For such large graphs, lumping is close to zooming of maps. Zooming provides users by a tool for work on various levels of model granularity [96] and gives a possibility to study interaction between processes at different levels of the hierarchy. The principle of semantic zooming [97^{*}] was used for development tools for navigations at different levels, similarly to geographic information systems [98^{*}] (Figure 4).

Figure 4



Principle of semantic zooming exploited by NaviCell tool [97*] for visualizing complex reaction networks in cancer biology. Semantic zooming can be considered as a simple application of lumping for gradual hiding the details of complex molecular mechanisms.

Conclusion

Three components of model reduction methodology are proved to be useful:

- Universal approaches developed for general finite-dimensional or even infinite dimensional systems (slow invariant manifolds, geometric singular perturbation theory, etc.). For them, chemical dynamics is an important source of challenges and applications.
- Thermodynamic approaches, which utilize the basic physical and chemical structures.
- Algebraic approaches based on analysis of reaction mechanism.

Interaction and mutual enrichment of these techniques will provide the future development of the efficient model reduction for better computational performance and deeper understanding of chemical dynamics.

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