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On the method of quasi-steady-state approximation

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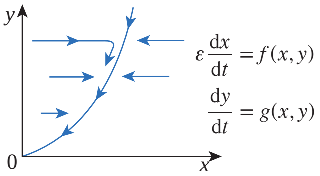
Sufficient conditions for the validity of the quasi-steady-state approximation widely used in chemical kinetics are considered by means of the qualitative geometric theory of differential equations with small parameters.



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Last year, the academic community celebrated the 150th anniversary of the birth of Max Bodenstein and the 125th anniversary of the birth of Nikolai Semenov, outstanding scientists who made a great contribution to chemical kinetics. Among other things, their names are associated with a common method for finding approximate solutions to systems of kinetic equations, the so-called quasi-steady-state approximation (QSSA). At the beginning of the last century, Bodenstein clearly formulated the QSSA for chemical systems,[1] and in the 1930s Semenov developed it for the case of chain reactions.[2] According to this method, the time derivatives corresponding to some intermediates are assumed to be zero during the course of the reaction. This procedure replaces the differential equations with algebraic ones, simplifying the mathematical part of the problem.

By and large, the QSSA had a profound and beneficial influence on the development of chemical kinetics, especially before the advent of computers in chemical practice, and usually gave satisfactory results, but as the method became widely used in chemical practice, difficulties arose so often that it is obvious, more stringent conditions were required for its applicability. One of the earliest and best known attempts to justify the QSSA was made by Frank-Kamenetsky,[3] who considered a chemical system about to reach a steady state and found that the lifetime of intermediates to which the QSSA could be applied, should be much less than the characteristic reaction time. Rice later came to the same conclusion.[4] This criterion did not contradict common sense and was intuitively understandable. However, later it was realized[5] that for the validity of the QSSA, these requirements are actually necessary conditions rather than sufficient ones, which are fundamentally required for a logically correct application.

The criteria for using the QSSA are often formulated as constraints imposed on concentrations: the concentration of the intermediate in question must be much lower than the concentration of the reactants. In his classic book,[6] Hammett articulated this clearly after considering the mechanism of consecutive first-order reactions involving only one intermediate and suggesting that this is also true in the case of more complex kinetic mechanisms. These criteria, formulated in terms of concentration, are usually given in up-to-date textbooks on chemical kinetics.[7–9]

Worthy of mention is the work by Benson,[10] in which, after considering several particular kinetic systems that are simple enough for an exact solution, he formulated the following conditions for justifying the QSSA. Namely, the rate of formation of the intermediate in question should be low compared with the rate of its removal by other processes. The conditions found this way were then speculatively extended to the general case that, of course, cannot be accepted as a rigorous approach. Note that the requirement for a low concentration of a fast intermediate is virtually equivalent to Benson’s criterion. In addition, Benson has clearly demonstrated the existence of an induction period of establishing a steady state. It is obvious that the shorter the induction period compared with the characteristic reaction time, the better the approximation given by the QSSA.

However, in the field of large complex kinetic schemes, the QSSA could give wrong results. For example, as was shown by Edelson[11] for a mechanism that models the explosion limits of carbon monoxide–oxygen mixtures and includes twenty four elementary reactions, the appropriate solution to the corresponding set of kinetic equations can be found by numerical methods rather than by the QSSA. The title of the paper by Farrow and Edelson[12] ‘The Steady-State Approximation: Fact or Fiction?’ (with emphasis on the latter) typifies the undeserved consequences for the reputation of the QSSA, which obviously arose due to the lack of well-defined mathematical criteria for the use of the QSSA. It is worth noting that the kinetics of chemical reactions, which includes some elementary processes, the time scales of which differ significantly, can be modeled by a set of differential equations, which are called stiff systems. The direct integration of such systems by numerical methods usually encountered certain difficulties.[13] Note that the QSSA was in fact intended to deal with stiff systems. When the stiffness problem has been generally overcome, the QSSA becomes almost irrelevant, at least for large kinetic systems. This was dramatized by the fact that in the 1970s interest in the QSSA began to wane as chemical kinetics fell out fashion.

This disappointment in the QSSA occurred despite the results obtained two decades earlier by Sayasov and Vasil’eva,[14] who approached the problem of the QSSA using the important achievement of asymptotic analysis, Tikhonov’s theorem.[15] By changing the variables in the system of differential equations corresponding to the general reaction mechanism, which involves some elementary processes with significantly different time scales, they transformed it into a set of differential equations, some of which contain small parameters multiplying time derivatives. These are the so-called singularly perturbed equations describing the behavior of short-lived intermediates. Thus, the use of the QSSA means zeroing out these small parameters that gives a zero-order approximation to the exact solution. Sayasov and Vasil'eva showed that the smallness of these parameters is not sufficient for obtaining a satisfactory approximation and that the right-hand side of the system of differential equations must also satisfy some additional conditions that were not taken into account earlier. Unfortunately, this work had almost no effect on the state of the art in physical chemistry at that time, probably because of excessive mathematical rigor.

Almost three decades later, a much more successful introduction of Tikhonov's theorem into chemical kinetics was made by Klonowski,[16] who considered several special cases of relatively small kinetic systems, in particular the classical Michaelis–Menten mechanism, as a clear illustration of the use of this mathematical theory to justify the QSSA. Since that time, Tikhonov's theorem has firmly taken its place at the heart of modern studies dealing with stiff kinetic systems.[17]

Thus, there exist well-founded criteria for the application of the QSSA, which remain important primarily from a didactic point of view, since the widely accepted basic results of chemical kinetics were obtained by the QSSA long before its proper justification. In addition, the QSSA is still a working tool in the study of kinetic mechanisms that involve only a few short-lived intermediates, while large kinetic systems are usually the subject of numerical methods.

So, it would seem that the story of developing the concept of the QSSA was successfully completed. Nevertheless, from time to time an old misconception appears in the literature, in which the idea of the QSSA reduces to the requirement that the short-lived intermediate in question has a rate approximately equal to zero for a considerable time interval. The purpose of these notes is to demonstrate that the misconception about the QSSA can be easily eliminated within the framework that is mathematically explicit and understandable to chemists with ordinary mathematical education and is based on the geometric representation of kinetic differential equations with singular perturbation developed by Mishchenko and Rozov;[18] as an illustration, the Michaelis–Menten mechanism will be considered.

To begin with, let us consider the following one-dimensional differential equation with the derivative multiplied by a small parameter:

$$\varepsilon \frac{\mathrm{d}x}{\mathrm{d}t} = f(x), \quad x(0) = x_0, \qquad (1)$$

where x is a scalar function of time, $f(x)$ is a continuous function differentiable at all points of the number line, ε is positive and small compared to unit. Being simple and clear, this artificial case has the main features of real kinetic schemes, to which the QSSA is applicable.

The geometric representation of the qualitative behavior of equation (1) is called its phase portrait, which in this case is simply a straight line (Figure 1), along which the image point representing equation (1) moves at a velocity $f(x)/\varepsilon$.[19] The roots of the equation $f(x) = 0$ are called fixed points. They completely determine the nature of the movement of the image point on the phase line, which obeys equation (1). From the point of view of the QSSA, we are only interested in one type of fixed points, the so-called attractors, where the image point remains for all t, once it gets there. Let $x = a > x_0$ be one of the roots, *i.e.*, $f(a) = 0$. One can specify the conditions under which this point is an attractor. In the neighborhood of $x = a$,

$$f(x) = (x - a)f'_x(a) + o(x - a). \qquad (2)$$

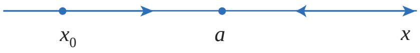

Figure 1 Phase portrait of a one-dimensional differential equation with an attractor at $x = a$ and an initial condition x_0 at $t = 0$.

So, if $f'_x < 0$, then the fixed point $x = a$ is stable. In other words, the solution of equation (1) $x = x(t,\varepsilon)$ is close to $x = a$ as $t \to \infty$ assuming that the interval (x_0,a) has no other fixed points.

It may take a short time for the phase point to come into the ε-neighborhood of $x = a$ from the point $x(0) = x_0$, since at each point of the x-axis located far enough from the attractor, the phase velocity $f(x)/\varepsilon$ can be very large depending on the smallness of ε. This time is in fact an induction period followed by a steady state corresponding to $x = a$.

Thus, the conditions under which the QSSA may be applied to equation (1) are as follows. Firstly, the value of ε must be small so that the induction period is short, and secondly, $f'_x(a) < 0$, which ensures that the fixed point will be an attractor.

At present the QSSA is primarily used in the study of small kinetic schemes, in particular the Michaelis–Menten scheme or something similar. It is worth noting that such systems are often encountered in photoreactions involving fast elementary processes.[20]

Once properly scaled, a reaction involving more than one step, such as

$$\text{Reactant} \rightleftarrows \text{Intermediate} \rightleftarrows \text{Product}, \qquad (3)$$

can be modeled by a set of differential equations in the form

$$\begin{aligned} \varepsilon \frac{\mathrm{d}x}{\mathrm{d}t} &= f(x,y), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= g(x,y), \end{aligned} \qquad (4)$$

where x and y are the scaled concentrations of the intermediate and reactant, respectively, as scalar functions of time t, while ε is a positive parameter, which is assumed to be small compared to unity. Initial conditions: $x = 0$ and $y = y_0$ at $t = 0$.

The constrained system that results from system (4) when $\varepsilon = 0$ is as follows:

$$\begin{aligned} 0 &= f(x,y), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= g(x,y). \end{aligned} \qquad (5)$$

The conditions, under which the solution of set (5) is a zero-order approximation to the solution of set (4) as $\varepsilon \to 0$, actually determine the validity of the QSSA.

Set (5) is not a normal differential system (the first equation is algebraic), so there is no solution with an arbitrary initial point, but only with the point that belongs to the curve $f(x,y) = 0$.[18] Therefore, rigorously speaking, we may directly compare the solutions of systems (4) and (5) only when the initial points of the former lie in the neighborhood of the curve. Stiff sets of differential equations that model the chemical mechanism do not hold because the initial point of any intermediate is zero and is normally far from the characteristic curve $f(x,y) = 0$. Nevertheless, under certain conditions, an arbitrary trajectory of system (4), starting at the point $(0, y_0)$, located at a finite distance from the curve, falls into its vicinity. In the case of a two-dimensional system, its phase trajectories can be easily represented geometrically, as shown in Figure 2. At each point of the phase plane (x,y) for system (4), there is a phase velocity vector:

$$v(x,y) = \left[\frac{1}{\varepsilon} f(x,y), g(x,y)\right]. \qquad (6)$$

If the initial point of the phase motion $(0, y_0)$ is at a finite distance from the characteristic curve, then as $\varepsilon \to 0$ the phase velocity vector has an infinitely large first component, while the second component is finite. Therefore, there occurs a rapid (almost instantaneous) change in the x coordinate, while the y coordinate remains almost constant, *i.e.*, the trajectory

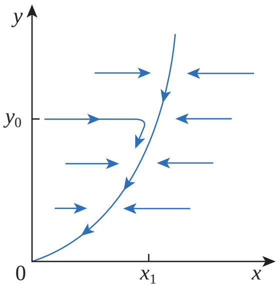

Figure 2 Schematic phase portrait of two-dimensional differential systems containing a small singular parameter ε. The directed curve represents a stable characteristic curve; the horizontal straight lines with arrows illustrate the trajectories in the phase plane at $\varepsilon \ll 1$. Initial conditions: $x = 0$ and $y = y_0$ at $t = 0$. The image point (x_1, y_0) is assumed to be close to the characteristic curve.

of system (4) is close to the trajectory of motion along the straight line $y = y_0$ according to the equation

$$\varepsilon \frac{\mathrm{d}x}{\mathrm{d}t} = f(x, y_0). \tag{7}$$

Thus, the problem actually reduces to the one-dimensional case considered above. In terms of the qualitative theory of differential equations with a small parameter,[18] the steady state corresponds to the slow motion of the phase point along the stable portion of the curve $f(x,y) = 0$. By definition, the totality of all points where $\partial f(x,y)/\partial x < 0$ is called a stable portion of the curve. At points where $\partial f/\partial x \geqslant 0$, the phase point may leave the curve, *i.e.*, the QSSA cannot be valid.

A highly reactive intermediate can be chosen as the QSSA variable, provided that the derivative with respect to its concentration on the right-hand side of the corresponding rate equation is negative. Upon decaying, the intermediate usually enters into a monomolecular or bimolecular elementary reaction (or both), which ensures the appearance of the corresponding negative terms on the right-hand side and the validity of the QSSA is normally fulfilled. However, in more complex cases, for example, in chain reactions, the possibility of the appearance of unstable points of the characteristic curve must not be ruled out.

By way of illustration, let us consider the classical Michaelis–Menten mechanism[21] for irreversible single-substrate enzymatic reactions:

$$\mathrm{E + S} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{ES} \xrightarrow{k_2} \mathrm{E + P}, \tag{8}$$

where S is the substrate, E is the enzyme, ES is the complex between them and P is the product. The differential equations corresponding to scheme (8) have the form

$$\begin{aligned} \frac{\mathrm{d}c}{\mathrm{d}t} &= k_1 es - (k_{-1} + k_2)c, \\ \frac{\mathrm{d}s}{\mathrm{d}t} &= -k_1 es + k_{-1}c. \end{aligned} \tag{9}$$

Here e, s and c are scalar functions of time denoting the current concentrations of the enzyme, substrate and complex between them, respectively. The differential equation for product concentration can be omitted due to the mass balance equation $s + c + p = s_0$, where p is the current product concentration and s_0 is the initial substrate concentration. Taking into account another mass balance equation, $e + c = e_0$, where e_0 is the initial concentration of the enzyme, we finally obtain the following system of rate equations:

$$\begin{aligned} \frac{\mathrm{d}c}{\mathrm{d}t} &= k_1(e_0 - c)s - (k_{-1} + k_2)c, \\ \frac{\mathrm{d}s}{\mathrm{d}t} &= -k_1(e_0 - c)s + k_{-1}c. \end{aligned} \tag{10}$$

There are initial values: $s(0) = s_0$ and $c(0) = 0$.

Introducing the characteristic reaction time $\tau = k_1 e_0 t$, *i.e.*, the dimensionless time measured during the reaction in units of $1/k_1 e_0$, and dividing both sides of the first equation of system (10) by the factor $(k_{-1} + k_2)$, we obtain

$$\begin{aligned} \varepsilon \frac{\mathrm{d}c}{\mathrm{d}\tau} &= \varepsilon s - \varepsilon \frac{s}{e_0} c - c, \\ \frac{\mathrm{d}s}{\mathrm{d}\tau} &= -s + \frac{c}{e_0} s + \frac{k_{-1}}{k_1 e_o} c. \end{aligned} \tag{11}$$

Here $\varepsilon = k_1 e_0/(k_{-1} + \mathrm{k}_2) = e_0/K_\mathrm{M}$, where $K_\mathrm{M} = (k_{-1} + k_2)/k_1$ is the Michaelis constant. It is entirely possible that the value of ε introduced in this way may be small.[21]

Introducing dimensionless concentrations $x = c/e_0$ and $y = s/e_0$, we finally obtain from system (11)

$$\begin{aligned} \varepsilon \frac{\mathrm{d}x}{\mathrm{d}\tau} &= \varepsilon y - \varepsilon yx - x, \\ \frac{\mathrm{d}y}{\mathrm{d}\tau} &= -y + yx + \frac{k_{-1}}{k_1 e_o} x. \end{aligned} \tag{12}$$

This scaling of variables is not unique, and its choice can play an important role in particular cases.[22]

The parameter ε enters the first equation of set (12) both on the left-hand side (singular perturbation) and on the right-hand side (regular perturbation), which seems to be a typical feature of common kinetic schemes.[23] Since the QSSA is a zero-order approximation of singular perturbation, we may keep the parameter ε on the right-hand side of the equation, so that the constrained system that results from system (12) is as follows:

$$\begin{aligned} 0 &= \varepsilon y - \varepsilon yx - x, \\ \frac{\mathrm{d}y}{\mathrm{d}\tau} &= -y + yx + \frac{k_{-1}}{k_1 e_o} x. \end{aligned} \tag{13}$$

The conditions under which the solution of system (13) is a zero-order approximation to the solution of system (12) actually determine the validity of the QSSA. It is worth noting that systems (12) and (13) correspond to systems (4) and (5), respectively.

The characteristic curve is defined by the equation $f(x,y) \equiv \varepsilon y - \varepsilon yx - x = 0$ and obviously $\partial f/\partial x < 0$ for all $y \geqslant 0$, so that the curve $y = x/[\varepsilon(1 - x)]$ is stable at all $x \geqslant 0$. The time required for the phase point to fall into the ε-vicinity of the curve determines the induction period τ_in of the establishment of a steady state. It can be estimated from the first equation of system (12) in the following way:

$$\tau_{in} \approx \varepsilon \int_0^{x_1} \frac{\mathrm{d}x}{\varepsilon y_0 - (\varepsilon y_0 + 1)x}, \tag{14}$$

where the upper limit, $x_1 = \varepsilon y_0/(1 + \varepsilon y_0) - \varepsilon$, defines a point on the straight line $y = y_0 \equiv s_0/e_0$ in the ε-vicinity of the curve (see Figure 2). From equation (14), it is easy to obtain

$$\tau_{in} \approx -\varepsilon \frac{1}{(1 + \varepsilon y_0)} \ln \varepsilon \left(1 + \frac{1}{\varepsilon y_0}\right). \tag{15}$$

As mentioned above, in order to be able to apply the QSAR, the induction period must be significantly less than the characteristic reaction time, *i.e.*, in dimensionless form $\tau_\mathrm{in} \ll 1$. Equation (15) was obtained under the assumption that the parameter ε is small, since the value of y_0 can vary over a wide range. If $\varepsilon y_0 \ll 1$, then it follows from equation (15) that $\tau_\mathrm{in} \approx \varepsilon \ln(1/y_0)$. In the case of $\varepsilon y_0 \gg 1$, $\tau_\mathrm{in} \approx (1/y_0)\ln(1/\varepsilon)$, in other words, $\tau_\mathrm{in} = o(1)$ independently of y_0. Thus, in the case of Michaelis–Menten scheme (8) with particular scaling of variables, a sufficient condition for the validity of the QSSA is $e_0/K_\mathrm{M} \ll 1$ in combination with the existence of a stable characteristic curve.

Generally, the QSSA for finding approximate solutions for small systems of kinetic differential equations may be applied provided that (i) there exists a small parameter that multiplies the derivative of the corresponding variable, singularly entering into the equation, and (ii) the right-hand sides of the differential equations corresponding to the intermediates in question should determine a stable characteristic curve. The fulfillment of these conditions allows to obtain a simple phase portrait (see Figure 2), which helps chemists to avoid common misinterpretation and misunderstanding of the QSSA.

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