Notes on QSS Reduction

1 Overview

The purpose of these notes is to describe the qss reduction in a systematic way, and then show several examples of how this works. We suppose that we have a differential equation of the form

$$\frac{du}{dt} = \frac{1}{\epsilon} Au + B(u),$$  \hspace{1cm} (1)

where $\epsilon << 1$. We assume that the eigenvalues of $A$ are non-positive. In order for there to be a separation of time scales, it must be that $A$ has a null-space. So we assume that the null-space of $A$ is spanned by $\{ \phi_i \}, i = 1, \ldots, k$, and that there are corresponding vectors $\{ \psi_i \}, i = 1, \ldots, k$, that span the nullspace of $A^T$, and form a biorthogonal set, $< \psi_i, \phi_j > = \delta_{ij}$.

To see the separation of time scales directly, we introduce a change of variables,

$$u = Pu + Qu = \sum_i a_i \phi_i + \chi$$  \hspace{1cm} (2)

where $Pu = \sum_i \alpha_i \phi_i$, $\alpha_i = < \psi_i, u >$, $Qu = u - Pu$. Notice that $P$ is a projection, with $Pu$ in the nullspace of $A$, and $Qu$ is orthogonal to the nullspace of $A^T$.

We project the equation (1) to find (multiply by $\psi_i$)

$$\frac{da_i}{dt} = \psi_i^T B(u).$$  \hspace{1cm} (3)

This is the slow-manifold equation. Next we note that $\frac{Qu}{dt} = \frac{du}{dt} - \frac{Pu}{dt}$, so that

$$\frac{d\chi}{dt} = \frac{1}{\epsilon} A\chi + B(u) - \sum_i \psi_i^T B(u) \phi_i.$$  \hspace{1cm} (4)

Now we are essentially done. The leading order qss approximation is $\chi = 0$ with slow dynamics given by

$$\frac{da_i}{dt} = \psi_i^T B(\sum_i a_i \phi_i).$$  \hspace{1cm} (5)

However, it is easy to get a better approximation by taking

$$\frac{1}{\epsilon} A\chi + B(\sum_i a_i \phi_i) - \sum_i \psi_i^T B(\sum_j a_j \phi_j) \phi_i$$  \hspace{1cm} (6)

in which case the slow equation becomes

$$\frac{da_i}{dt} = \psi_i^T B \left( \sum_i a_i \phi_i - \epsilon A^\dagger \left( B(\sum_i a_i \phi_i) - \sum_i \psi_i^T B(\sum_j a_j \phi_j) \phi_i \right) \right).$$  \hspace{1cm} (7)

Notice that this analysis assumes that $\phi_i$ are independent of time. If they are not independent of time, a similar argument still applies, but with some extra terms.
Figure 1: Model of the RyR. R and RI are closed states, O is the open state, and I is the inactivated state.

2 Examples

2.1 RyR Kinetics

Consider the 4-state chemical reaction network shown in Fig.1

We assume that $k_1 >> k_2$ and $k_{-1} >> k_{-2}$. To simplify the notation, we set $c = 1$. The master equation for this network can be written in the form of (1) by first rescaling $k_{\pm 1} \rightarrow \epsilon k_{\pm 1}$ for some fixed small number $\epsilon$. We don’t specify it completely, because we want to allow $k_1, k_2, k_{-1}$ and $k_{-2}$ to be time varying.

\[
\begin{align*}
    u &= \begin{pmatrix} P_{00} \\ P_{10} \\ P_{01} \\ P_{11} \end{pmatrix}, \\
    A &= \begin{pmatrix} -k_1 & k_{-1} & 0 & 0 \\ k_1 & -k_{-1} & 0 & 0 \\ 0 & 0 & -k_1 & k_{-1} \\ 0 & 0 & k_1 & -k_{-1} \end{pmatrix}, \\
    B &= \begin{pmatrix} -k_2 & 0 & k_{-2} & 0 \\ 0 & -k_2 & 0 & k_{-2} \\ k_2 & 0 & -k_{-2} & 0 \\ 0 & k_2 & 0 & -k_{-2} \end{pmatrix}
\end{align*}
\]

(8)

where the identification of states is $R = \{00\}$, $RI = \{01\}$, $O = \{10\}$, $I = \{11\}$.

The decomposition of the equations uses the vectors

\[
\begin{align*}
    \phi_1 &= \begin{pmatrix} \kappa_{-1} \\ \kappa_1 \\ 0 \\ 0 \end{pmatrix}, \\
    \phi_2 &= \begin{pmatrix} 0 \\ 0 \\ \kappa_{-1} \\ \kappa_1 \end{pmatrix}, \\
    \phi_3 &= \begin{pmatrix} 1 \\ -1 \\ 0 \\ 0 \end{pmatrix}, \\
    \phi_4 &= \begin{pmatrix} 0 \\ 0 \\ 1 \\ -1 \end{pmatrix}
\end{align*}
\]

(9)

where $\kappa_{\pm 1} = \frac{k_{\pm 1}}{k_1 + k_{-1}}$, and

\[
\begin{align*}
    \psi_1 &= \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \end{pmatrix}, \\
    \psi_2 &= \begin{pmatrix} 0 \\ 0 \\ 1 \\ 1 \end{pmatrix}, \\
    \psi_3 &= \begin{pmatrix} \kappa_1 \\ \kappa_{-1} \\ 0 \\ 0 \end{pmatrix}, \\
    \psi_4 &= \begin{pmatrix} 0 \\ 0 \\ \kappa_1 \\ -\kappa_{-1} \end{pmatrix}
\end{align*}
\]

(10)

Notice that $\phi_1, \phi_2$ span the nullspace of $A$, $\phi_3, \phi_4$ span the non-zero eigenspace of $A$, $\psi_1, \psi_2$ span the nullspace of $A^T$, and $\psi_3, \psi_4$ span the nonzero eigenspace of $A^T$.

We define $y_1 = P_{00} + P_{10}$, $y_2 = P_{01} + P_{11}$, and and learn that (multiply by $\psi_1$ and $\psi_2$)

\[
\begin{align*}
    \frac{dy_1}{dt} &= -k_2 y_1 + k_{-2} y_2, \\
    \frac{dy_2}{dt} &= k_2 y_1 - k_{-2} y_2
\end{align*}
\]

(11)
which describes the slow kinetics. The fast kinetics follow (from multiplication by $\psi_3$, and $\psi_4$)

$$\left( \begin{array}{c} \kappa_1 \frac{dP_{00}}{dt} - \kappa_{-1} \frac{dP_{10}}{dt} \\ \kappa_1 \frac{dP_{01}}{dt} - \kappa_{-1} \frac{dP_{11}}{dt} \end{array} \right) = -\frac{1}{\epsilon} \left( \begin{array}{c} z_1 \\ z_2 \end{array} \right) + \left( \begin{array}{cc} -k_2 & k_{-2} \\ k_2 & -k_{-2} \end{array} \right) \left( \begin{array}{c} z_1 \\ z_2 \end{array} \right)$$

(12)

where $z_1 = \kappa_1 P_{00} - \kappa_{-1} P_{10}$, and $z_2 = \kappa_1 P_{00} - \kappa_{-1} P_{10}$.

Thus, the leading order qss approximation has $z_1 = z_2 = 0$, or $\kappa_1 P_{00} - \kappa_{-1} P_{10} = 0$, and $\kappa_1 P_{00} - \kappa_{-1} P_{10} = 0$. That is,

$$
\begin{align*}
P_{00} &= y_1 \frac{\kappa_{-1}}{\kappa_1 + \kappa_{-1}}, & P_{10} &= y_1 \frac{\kappa_1}{\kappa_1 + \kappa_{-1}}, & P_{01} &= y_2 \frac{\kappa_{-1}}{\kappa_1 + \kappa_{-1}}, & P_{11} &= y_2 \frac{\kappa_1}{\kappa_1 + \kappa_{-1}}.
\end{align*}
$$

(13)

2.2 Adiabatic Reduction for Master Equations

This same technology can be used to find the slow evolution of drift-jump stochastic processes. We suppose that the transitions between $x_k$ states are fast. If this is the case, then we can write the master equation system as

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial y} (Fp) + \frac{1}{\epsilon} Ap.$$  

(14)

Now, it must be that the matrix $A$ has a zero eigenvalue with eigenvector $\phi$. The corresponding left eigenvector is $\psi$ with entries $(\psi_j) = 1$. We assume that $\langle \phi, \psi \rangle = 1$. Using these, we split $p$ into two parts

$$p = v\phi + w$$

(15)

where $\langle p, \psi \rangle = v$, and $\langle w, \psi \rangle = 0$. It follows that

$$\frac{\partial v}{\partial t} = -\psi^T \frac{\partial}{\partial y} (F(v\phi + w)), $$

(16)

and

$$\frac{\partial w}{\partial t} = \frac{1}{\epsilon} Aw - \frac{\partial}{\partial y} (Fp) + \psi^T \frac{\partial}{\partial y} (Fp)\phi.$$  

(17)

Here, the fast behavior of $w$ is evident, so we take $w$ to be in quasi-steady state. Thus, we take

$$Aw = \epsilon \frac{\partial}{\partial y} (vF\phi) - \epsilon \psi^T \frac{\partial}{\partial y} (vF\phi)\phi + O(\epsilon^2).$$

(18)

This equation can be solved uniquely for $w$ subject to the constraint $\psi^T w = 0$; we denote this as

$$w = \epsilon A^\perp \frac{\partial}{\partial y} (vF\phi) - \epsilon \psi^T \frac{\partial}{\partial y} (vF\phi)\phi + O(\epsilon^2),$$

(19)

where $A^\perp$ is the inverse of the properly constrained $A$. Consequently,

$$\frac{\partial v}{\partial t} = -\frac{\partial}{\partial y} (\psi^T Fv\phi) - \frac{\partial}{\partial y} \left( \epsilon \psi^T FA^\perp \left( \frac{\partial}{\partial y} (vF\phi) - \psi^T \frac{\partial}{\partial y} (vF\phi)\phi \right) \right),$$

(20)
2.3 Jump Velocity Processes

Consider the simple example of a stochastic differential equation
\[
\frac{dy}{dt} = kx, \tag{21}
\]
where \( x \) is either 0 or 1, with transition rates \( \alpha \) and \( \beta \). The F-P equation is
\[
\frac{\partial p}{\partial t} = \alpha q - \beta p - \frac{\partial kp}{\partial y}, \tag{22}
\]
\[
\frac{\partial q}{\partial t} = \beta p - \alpha q. \tag{23}
\]
We can reduce this to a single pde by observing that \( \frac{\partial q}{\partial t} = -\frac{\partial p}{\partial t} - \frac{\partial ap}{\partial y} \) so that
\[
p_{tt} = -(\alpha + \beta)p_{t} - \alpha kp_{y} - kp_{ty}. \tag{24}
\]
Suppose that \( \alpha \) and \( \beta \) are large compared to \( k \). Then the exchange between states is fast relative to the rate of change of \( y \), and we should be able to do a qss reduction. To do so, we introduce dimensionless time (set \( k = 1 \)) and let \( \epsilon = \frac{1}{\alpha + \beta} \), and introduce \( a = \frac{\alpha}{\alpha + \beta} \) and \( b = \frac{\beta}{\alpha + \beta} \), so that \( a + b = 1 \). In terms of these variables, the F-P equations are
\[
\frac{\partial p}{\partial t} = \frac{1}{\epsilon}(aq - bp) - \frac{\partial p}{\partial y}, \tag{25}
\]
\[
\frac{\partial q}{\partial t} = \frac{1}{\epsilon}(bp - aq). \tag{26}
\]
We introduce the change of variables
\[
v = p + q, \quad w = bp - aq, \tag{27}
\]
so that
\[
p = av + w, \quad q = bv - w. \tag{28}
\]
In terms of these variables the F-P equations are
\[
\frac{\partial v}{\partial t} = -\frac{\partial av}{\partial y} - \frac{\partial w}{\partial y}, \tag{29}
\]
\[
\frac{\partial w}{\partial t} = -\frac{1}{\epsilon} w - b\frac{\partial av}{\partial y} - b\frac{\partial w}{\partial y}. \tag{30}
\]
Now we see the obvious fast-slow separation and take \( w \) to be in quasi-steady state, so that
\[
w = -\epsilon b\frac{\partial av}{\partial y} + O(\epsilon^2), \tag{31}
\]
from which it follows that
\[
\frac{\partial v}{\partial t} = -\frac{\partial av}{\partial y} + \frac{\partial}{\partial y}(\epsilon b\frac{\partial av}{\partial y}) + O(\epsilon^2), \tag{32}
\]
which is the standard F-P equation we seek.
2.3.1 More generally

For the more general problem

\[ \frac{dy}{dt} = xf(y) - g(y), \tag{33} \]

the F-P equations are

\[ \frac{\partial p}{\partial t} = \frac{1}{\varepsilon} (aq - bp) - \frac{\partial}{\partial y} ((f - g)p), \tag{34} \]
\[ \frac{\partial q}{\partial t} = \frac{1}{\varepsilon} (bp - aq) + \frac{\partial}{\partial y} (gq). \tag{35} \]

We now introduce the change of variables (27) and find

\[ \frac{\partial v}{\partial t} = -\frac{\partial}{\partial y} ((af - g)v + fw), \tag{36} \]
\[ \frac{\partial w}{\partial t} = -\frac{1}{\varepsilon} w - a \frac{\partial}{\partial y} (gq) - b \frac{\partial}{\partial y} ((f - g)p). \tag{37} \]

Again, the fast-slow separation is apparent and we take \( w \) to be in quasi-steady state, so that

\[ w = \varepsilon (-a \frac{\partial}{\partial y} (gbv) - b \frac{\partial}{\partial y} ((f - g)av)) + O(\varepsilon^2), \tag{38} \]

from which it follows that

\[ \frac{\partial v}{\partial t} = -\frac{\partial}{\partial y} ((af - g)v) + \frac{\partial}{\partial y} \left( \varepsilon f \frac{\partial}{\partial y} (fav) + \varepsilon fgv \frac{\partial}{\partial y} \right) + O(\varepsilon^2), \tag{39} \]

which is the F-P equation we seek.