Enzyme Kinetics: sCMT reduction of the chemical Langevin equation (CLE)

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June 6, 2023

The problem statement (more or less)

The CLE for the Michaelis-Menten reaction mechanism is

$$
\begin{pmatrix} \dot{s} \\ \dot{c} \end{pmatrix} = \begin{pmatrix} -k_1(e_0-c)s + k_{-1}c \\ k_1(e_0-c)s - (k_{-1}+k_2)c \end{pmatrix} + \sigma \begin{pmatrix} -\sqrt{k_1(e_0-c)s} & \sqrt{k_{-1}c} & 0 \\ \sqrt{k_1(e_0-c)s} & -\sqrt{k_{-1}c} & -\sqrt{k_2c} \end{pmatrix} \cdot \begin{pmatrix} \zeta_1 \\ \zeta_2 \\ \zeta_3 \end{pmatrix}. \tag{1}
$$

For small e_0, we rewrite $e_0 \to \varepsilon e_0$, in express perturbation form:

$$
\begin{pmatrix} \dot{s} \\ \dot{c} \end{pmatrix} = \begin{pmatrix} k_1 s + k_{-1} \\ -k_1 s - k_{-1} - k_2 \end{pmatrix} c + \varepsilon \begin{pmatrix} -k_1 e_0 s \\ k_1 e_0 s \end{pmatrix} + \sigma \begin{pmatrix} -\sqrt{k_1(\varepsilon e_0 - c)s} & \sqrt{k_{-1}c} & 0 \\ \sqrt{k_1(\varepsilon e_0 - c)s} & -\sqrt{k_{-1}c} & -\sqrt{k_2c} \end{pmatrix} \cdot \begin{pmatrix} \zeta_1 \\ \zeta_2 \\ \zeta_3 \end{pmatrix}. \tag{2}
$$

Observe that the critical manifold, $\mathcal{M}_0$, is

$$
\mathcal{M}_0 := \{(s,c) \in \mathbb{R}^2 : c = 0\} \tag{3}
$$

which is identical to the s-axis. Hence, the critical manifold coincides with a coordinate subspace, and this is common in enzyme kinetics. The projection matrix, $\Pi : \mathbb{R}^2 \mapsto T_x \mathcal{M}_0$ is

$$
\Pi := \begin{pmatrix} 1 & \gamma \\ 0 & 0 \end{pmatrix}, \qquad \gamma := \frac{s + K_S}{s + K_M} \tag{4}
$$

where $K_S := k_{-1}/k_1$ and $K_M := (k_{-1}+k_2)/k_1$. A straightforward (and naive) projection onto the critical manifold yields the reduced equation

$$
\dot{s} = -\frac{k_2 \varepsilon e_0 s}{s + K_M} + -\frac{\sigma K}{s + K_M}\sqrt{k_1(\varepsilon e_0)s} \cdot \zeta_1, \tag{5}
$$

where $K := k_2/k_1$.

Remark 1. *Note that the white noise terms ζ_2, ζ_2 are not ignored; rather, they vanish upon evaluating*

$$
\sigma \cdot \begin{pmatrix} 1 & \dfrac{s+K_S}{s+K_M} \\ 0 & 0 \end{pmatrix} \cdot \begin{pmatrix} -\sqrt{k_1(\varepsilon e_0 - c)s} & \sqrt{k_{-1}c} & 0 \\ \sqrt{k_1(\varepsilon e_0 - c)s} & -\sqrt{k_{-1}c} & -\sqrt{k_2c} \end{pmatrix} \cdot \begin{pmatrix} \zeta_1 \\ \zeta_2 \\ \zeta_3 \end{pmatrix} \Bigg|_{c=0} = \sigma \cdot \begin{pmatrix} -\sqrt{k_1 \varepsilon e_0 s} \cdot \zeta_1 \\ 0 \end{pmatrix} \tag{6}
$$

There are some serious concerns with this reduction:

1. Is this correct? It is not obvious to JE that it is. I suspect it is incorrect. What is TR's opinion?

2. Is there a drift term? The critical manifold as zero curvature; however, the critical manifold differs from the QSS variety (the c-nullcline), whose graph, $\mathcal{G}$, is

$$\mathcal{G} := \{(s, c) \in \mathbb{R}^2 : c = e_0 s / (K_M + s)\}$$

and has curvature! This is something that is often left out in the literature. Critical manifold may be void of curvature, but that doesn't mean that the QSS variety is too.

3. The *local* behavior of the system is that of one in standard form. This comes from the *degenerate* scaling, $e_0 \to \varepsilon e_0$ and $c \to \varepsilon c$, which yields:

$$\dot{s} = \varepsilon[-k_1(e_0 - c)s + k_{-1}c], \tag{7a}$$
$$\dot{c} = k_1(e_0 - c)s - (k_{-1} + k_2)c, \tag{7b}$$

which brings the system into standard form. Formal, rigorous justification for this rescaling (from the toolbox of geometric singular perturbation theory) comes from a cylindrical blow-up (unpublished result from JE). If one appeals to the degenerate scaling, then the flow field has zero curvature and there is zero angular variation.

4. On the other hand, if we do not appeal to the degenerate scaling, we obtain the first integral,

$$s + c + K \cdot \ln\left[\frac{s + K_S}{s_0 + K_S}\right] = const. \tag{8}$$

The curves (8) terminate (approach as $t \to \infty$) at the base points of the critical manifold (3). Thus, in the singular limit, the flow field has both curvature and variation. The difficult part is that the local behavior doesn't ever really 'feel' this, because conservation of enzyme traps trajectories in an $\mathcal{O}(\varepsilon)$ "tube" around the critical manifold. This is one reason why the degenerate scaling works.

The reason the QSS variety and the critical manifold differ is ultimately due to the fact that the system is not in standard form for small e_0, and the first term in the asymptotic expansion of slow manifold is zero. The QSS variety (c-nullcline) is a first order correction to the critical manifold. This is straightforward to see from CMT.

To summarize: What *is* the reduced CLE for small e_0? This is an open problem and a difficult problem. Reduction methodologies are useful because critical manifolds that coincide with coordinate axes are common in chemical kinetics. From what I can tell, nobody has investigated this...

The degenerate scaling

Let's proceed to compute the reduced CLE via the degenerate scaling (which is commonly used in the literature; see for example Segel and Slemrod).

$$\dot{s} = \varepsilon[-k_1(e_0 - c)s + k_{-1}c], \tag{9a}$$
$$\dot{c} = k_1(e_0 - c)s - (k_{-1} + k_2)c, \tag{9b}$$

In perturbation form we obtain

$$\begin{pmatrix} \dot{s} \\ \dot{c} \end{pmatrix} = \begin{pmatrix} 0 \\ 1 \end{pmatrix} \cdot [k_1(e_0 - c) - (k_{-1} + k_2)c] + \varepsilon \begin{pmatrix} 1 \\ 0 \end{pmatrix} \cdot [-k_1(e_0 - c)s + k_{-1}c] \ + ...$$

$$... \ \sigma \cdot \sqrt{\varepsilon} \cdot \begin{pmatrix} -\sqrt{k_1(e_0 - c)s} & \sqrt{k_{-1}c} & 0 \\ \sqrt{k_1(e_0 - c)s} & -\sqrt{k_{-1}c} & -\sqrt{k_2c} \end{pmatrix} \cdot \begin{pmatrix} \zeta_1 \\ \zeta_2 \\ \zeta_3 \end{pmatrix}. \tag{10}$$

Again, there is flow field no curvature, no variation, and the curvature of the slow manifold practically negligible (even if it wasn't, it wouldn't introduce a bias. The reduced CLE is

$$\dot{s} = -\frac{\varepsilon V s}{K_M + s} + \sigma \cdot \sqrt{\varepsilon} \cdot [-\sqrt{(k_1(e_0 - c)s} \cdot \zeta_1 + \sqrt{k_{-1}c} \cdot \zeta_2]|_{c = e_0 s/(K_M + s)} \tag{11}$$

which is completely different from (5)! Here we see a huge difference between the deterministic and the stochastic reductions methodologies: it makes a huge difference as to how one "introduces" a small parameter into the equations. In the deterministic regime it appears not to matter (most of the time). This appears to not be the case in the stochastic regime, as different scalings can result in extremely different CLEs.