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Supporting Information for "The Stochastic Quasi-Steady-State Assumption: Reducing the Model but Not the Noise"

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We report in the statement of some results and the proofs omitted from the paper "The Stochastic Quasi-Steady-State Assumption: Reducing the Model but Not the Noise" [3]. All numberings are referred to the paper [3].

S1 Example 1: Derivation for Pap operon regulation

Dividing both sides of equations (1)–(4) of the paper by $r_1 + r_3$ and defining $\epsilon = 1/(r_1 + r_3)$ gives

$$\epsilon \frac{dP_1}{dt} = -P_1 + \epsilon r_2 P_2 + \epsilon r_4 P_3 \tag{1}$$
$$\epsilon \frac{dP_2}{dt} = -\epsilon(r_2 + r_5)P_2 + K_1 P_1 + \epsilon r_6 P_4 \tag{2}$$
$$\epsilon \frac{dP_3}{dt} = -\epsilon(r_4 + r_7)P_3 + K_3 P_1 + \epsilon r_8 P_4 \tag{3}$$
$$\epsilon \frac{dP_4}{dt} = -\epsilon(r_6 + r_8)P_4 + \epsilon r_5 P_2 + \epsilon r_7 P_3 \tag{4}$$
$$\tag{5}$$

in which $K_1 = r_1/(r_1 + r_3)$ and $K_3 = r_3/(r_1 + r_3)$ are $O(1)$ terms.

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S1.1 Fast time scale solution

In the fast time scale we rescale time t to $\tau = t/\epsilon$. Using τ we rewrite (1)–(4) on the fast time scale as

$$\frac{d\hat{P}_1}{d\tau} = -\hat{P}_1 + \epsilon r_2 \hat{P}_2 + \epsilon r_4 \hat{P}_3 \tag{6}$$

$$\frac{d\hat{P}_2}{d\tau} = -\epsilon(r_2 + r_5)\hat{P}_2 + K_1\hat{P}_1 + \epsilon r_6 \hat{P}_4 \tag{7}$$

$$\frac{d\hat{P}_3}{d\tau} = -\epsilon(r_4 + r_7)\hat{P}_3 + K_3\hat{P}_1 + \epsilon r_8 \hat{P}_4 \tag{8}$$

$$\frac{d\hat{P}_4}{d\tau} = -\epsilon(r_6 + r_8)\hat{P}_4 + \epsilon r_5\hat{P}_2 + \epsilon r_7 \hat{P}_3 \tag{9}$$

$$\tag{10}$$

in which we denote probability on the fast time scale by $\hat{P}_i$. We expand $\hat{P}_i$ in a power series

$$\hat{P}_i = \hat{W}_{i0} + \epsilon\hat{W}_{i1} + \epsilon^2\hat{W}_{i2} + O(\epsilon^3) \tag{11}$$

Substituting (11) into (6) and retaining terms up to order ϵ^1 give

$$\frac{d\hat{W}_{10}}{d\tau} + \epsilon\frac{d\hat{W}_{11}}{d\tau} + \cdots = -(\hat{W}_{10} + \epsilon\hat{W}_{11} + \cdots) + \epsilon r_2(\hat{W}_{20} + \epsilon\hat{W}_{21} + \cdots) + \epsilon r_4(\hat{W}_{30} + \epsilon\hat{W}_{31} + \cdots) \tag{12}$$

Comparing $O(\epsilon^0)$ terms in (12) gives

$$\frac{d\hat{W}_{10}}{d\tau} = -\hat{W}_{10} \tag{13}$$

with initial condition $\hat{W}_{10}(\tau = 0) = 1$. The solution of (13) is

$$\hat{W}_{10} = e^{-\tau} \tag{14}$$

which is the equation (5) of the paper. Rewriting equation (7) using equation (11) gives

$$\frac{d\hat{W}_{20}}{d\tau} + \epsilon\frac{d\hat{W}_{20}}{d\tau} + \cdots = -\epsilon(r_2 + r_5)(\hat{W}_{20} + \epsilon\hat{W}_{21} + \cdots) + K_1(\hat{W}_{10} + \epsilon\hat{W}_{11} + \cdots) + \epsilon r_6(\hat{W}_{40} + \epsilon\hat{W}_{41} + \cdots) \tag{15}$$

Comparing $O(\epsilon^0)$ terms from (15) gives

$$\frac{d\hat{W}_{20}}{d\tau} = K_1\hat{W}_{10} \tag{16}$$

with initial condition $\hat{W}_{20}(\tau = 0) = 0$. We substitute $\hat{W}_{10}$ from (14) into (16) and solve the differential equation to obtain

$$\hat{W}_{20} = K_1(1 - e^{-\tau}) \tag{17}$$

which is the equation (6) of the paper. We obtain the expansions of the probabilities of states g_3 and g_4, i.e., $\hat{W}_{30}$ and $\hat{W}_{40}$, analogously.

S1.2 Slow time scale solution

In (1) we substitute expansion of P_i, $1 \leq i \leq 4$

$$P_i = W_{i0} + \epsilon W_{i1} + \epsilon^2 W_{i2} + O(\epsilon^3) \tag{18}$$

giving

$$\epsilon\Big(\frac{dW_{10}}{dt} + \epsilon\frac{dW_{11}}{dt} + \cdots\Big) = (-W_{10} + \epsilon W_{11} + \cdots) + \epsilon r_2(W_{20} + \epsilon W_{21} + \cdots) + \epsilon r_4(W_{30} + \epsilon W_{31}) \tag{19}$$

Collecting $O(\epsilon^0)$ terms from (19) gives

$$W_{10} = 0 \tag{20}$$

which is equation (9) of the paper. Next we collect $O(\epsilon^1)$ terms from (19) to obtain

$$W_{11} = r_2 W_{20} + r_4 W_{30} \tag{21}$$

A better approximation for the probability of state g_1,$\tilde{P}_1$, is obtained by approximating P_1 up to $O(\epsilon)$.

$$\tilde{P}_1 = W_{10} + \epsilon W_{11} \tag{22}$$

Using equations (20) and (21) in equation (22) gives

$$\tilde{P}_1 = \epsilon(r_2 W_{20} + r_4 W_{30}) \tag{23}$$

which is equation (13) of the paper.

Next we substitute (18) into (2) to obtain

$$\epsilon\Big(\frac{dW_{20}}{dt} + \epsilon\frac{dW_{21}}{dt} + \cdots\Big) = -\epsilon(r_2 + r_5)(W_{20} + \epsilon W_{21} + \cdots) + K_1(W_{10} + \epsilon W_{11} + \cdots) + \epsilon r_6(W_{40} + \epsilon W_{41} + \cdots) \tag{24}$$

Comparison of $O(\epsilon^0)$ terms from (24) leads to equation (20). Thus comparison of $O(\epsilon^0)$ terms from (24) does not lead to any new information. Comparing $O(\epsilon^1)$ terms from (24) we obtain:

$$\frac{dW_{20}}{dt} = -(r_2 + r_5)W_{20} + r_6 W_{40} + K_1 W_{11} \tag{25}$$

Substituting W_{11} from (21) into (25) gives

$$\frac{dW_{20}}{dt} = -[\tilde{r_1} + r_5]W_{20} + \tilde{r_2} W_{30} + r_6 W_{40} \tag{26}$$

which is the same as equation (10) of the paper. Evolution equations for W_{30} and W_{40} can be obtained similarly.

S2 Example 2: Derivations for robustness to noise in a biochemical oscillator.

S2.1 sQSPA reduction

We consider reaction network (15) of the paper These reactions include the transcription events to form M_A, translation to form A, and degradation of M_A. These reactions do not lead to change in the populations of species D_A and D'_A, hence we write $P(D_A, D'_A, M_A, A)$ as $P(M_A, A)$.The master equation for this system is

$$\frac{dP(M_A,A)}{dt} = \alpha_A D_A P(M_A-1,A) + \alpha'_A D'_A P(M_A-1,A) + \delta_{MA}(M_A+1)P(M_A+1,A) + \beta_A M_A P(M_A, A-1) - \left[\alpha_A D_A + \alpha'_A D'_A + (\delta_{MA}+\beta_A)M_A\right] P(M_A,A) \quad (27)$$

When the condition $\beta_A, \delta_{MA} \gg \alpha_A, \alpha'_A$ holds, the mRNA species M_A is a QSSA species. We further define

$$\epsilon = \frac{1}{(\beta_A+\delta_{MA})} \qquad \bar{\delta}_{MA} = \epsilon\delta_{MA} \qquad \bar{\beta}_A = \epsilon\beta_A$$

Multiplying (27) with ϵ gives us

$$\epsilon\frac{dP(M_A,A)}{dt} = \epsilon(\alpha_A D_A + \alpha'_A D'_A)P(M_A-1,A) + \bar{\delta}_{MA}(M_A+1)P(M_A+1,A) + \bar{\beta}_A M_A P(M_A,A-1) - \left[\epsilon(\alpha_A D_A + \alpha'_A D'_A) + (\bar{\delta}_{MA}+\bar{\beta}_A)M_A\right] P(M_A,A) \quad (28)$$

We expand $P(M_A, A)$ in a power series

$$P(M_A,A) = W_0(M_A,A) + \epsilon W_1(M_A,A) + \epsilon^2 W_2(M_A,A) + \cdots \quad (29)$$

Then by grouping like powers of ϵ in (28), we obtain

$$\epsilon^0: \quad 0 = \bar{\delta}_{MA}(M_A+1)W_0(M_A+1,A) + \bar{\beta}_A M_A W_0(M_A,A-1) - \left(\bar{\delta}_{MA}+\bar{\beta}_A\right) M_A W_0(M_A,A) \quad (30)$$

Expressing this result for $M_A = 0, 1, \ldots$ yields

$$W_0(M_A,A) = 0 \quad \text{for } M_A > 0 \quad \text{for all } A \quad (31)$$

Similarly, equating terms of $O(\epsilon^1)$ yields

$$\epsilon^1, M_A = 0: \quad \frac{dW_0(0,A)}{dt} = \bar{\delta}_{MA} W_1(1,A) - \left(\alpha_A D_A + \alpha'_A D'_A\right) W_0(0,A) \quad (32)$$

$$\epsilon^1, M_A = 1: \quad W_1(1,A) = \bar{\beta}_A W_1(1,A-1) + (\alpha_A D_A + \alpha'_A D'_A)W_0(0,A) \quad (33)$$

Solving the last equation for $W_1(1, A)$ gives

$$W_1(1,A) = (\alpha_A D_A + \alpha'_A D'_A)W_0(0,A) + \sum_{j=1}^{A} \bar{\beta}_A^j (\alpha_A D_A + \alpha'_A D'_A)W_0(0,A-j)$$

Substituting this result into (32) gives

$$\frac{dW_0(0,A)}{dt} = \bar{\delta}_{MA}\sum_{j=1}^{A} \bar{\beta}_A^j(\alpha_A D_A + \alpha'_A D'_A)W_0(0,A-j) - \bar{\beta}_A(\alpha_A D_A + \alpha'_A D'_A)W_0(0,A) \quad (34)$$

The catalytic reactions in the paper, reaction sets (16) and (17), follow from this equation.

S2.2 Deterministic quasi steady state classical (dQC) reduction

Again we consider the reaction network (15) of the paper. The master equation describing the species M_A can be written as:

$$\frac{dM_A}{dt} = \alpha_A D_A + \alpha'_A D'_A - \delta_{MA} M_A - \beta_A M_A \tag{35}$$

Under the condition $\beta_A, \delta_{MA} \gg \alpha_A, \alpha'_A, \delta_A$, M_A is a QSSA species. To apply dQC we set left hand side of equation (35) to 0 to obtain following expression for the population of M_A.

$$M_A = \frac{\alpha_A D_A + \alpha'_A D'_A}{\delta_{MA} + \beta_A} \tag{36}$$

The rate of formation of A is equal to the rate of last reaction of the network

$$\frac{dA}{dt} = \beta_A M_A = \bar{\beta}_A(\alpha_A D_A + \alpha'_A D'_A) \tag{37}$$

Since M_A is already removed from the network. The only species that changes with time is species A. Equations (36) and (37) give rise to the dQC reduced reactions (18) and (19) of the paper.

S3 Example 3: Derivation for Fast fluctuation

We apply Ω expansion as outlined by van Kampen [4] on the master equation of reactions (20) – (22) of the paper. The master equation for these reactions is

$$\begin{aligned}\frac{dP(a,c,g)}{dt} =& \frac{k_1}{\Omega}(a+1)gP(a+1,c-1,g) + \frac{k_2}{\Omega}(c+1)(g-1)P(a-1,c+1,g-1) \\ &+ \frac{k_3}{\Omega}(g+1)gP(a,c,g+1) - \left(\frac{k_1}{\Omega}ag + \frac{k_2}{\Omega}cg + \frac{k_3}{\Omega}g(g-1)\right)P(a,c,g)\end{aligned} \tag{38}$$

There are two phases of time evolution of the species population. In the first phase, species G increases and species A and C start fluctuating. After species G has risen above a certain threshold value, we switch the simulation methodology to the SSA-Ω approach. We write g as a continuous random variable:

$$g = \Omega\phi_G + \Omega^{1/2}\xi \tag{39}$$

where ϕ_G is the deterministic mean concentration of species G in the regime of SSA-Ω and $\Omega^{1/2}\xi$ is the noise in G. For the transformed variable g, the probability $P(a,c,g)$ corresponds to $\Pi(a,c,\xi)$. In (38) we can write

$$\frac{dP(a,c,g)}{dt} = \frac{\partial\Pi(a,c,\xi)}{\partial t} - \Omega^{1/2}\frac{d\phi_g}{dt}\frac{\partial\Pi(a,c,\xi)}{\partial\xi}$$

Under this change of variables, (38) becomes

$$\begin{aligned}&\frac{\partial\Pi(a,c,\xi)}{\partial t} - \Omega^{1/2}\frac{d\phi_g}{dt}\frac{\partial\Pi(a,c,\xi)}{\partial\xi} \\ &= \frac{k_1}{\Omega}(a+1)(\Omega\phi_G + \Omega^{1/2}\xi)\Pi(a+1,c-1,\xi) \\ &+ \frac{k_2}{\Omega}(c+1)[1-\Omega^{-1/2}\frac{\partial}{\partial\xi}+\Omega^{-1}\frac{\partial^2}{\partial\xi^2} - \cdots](\Omega\phi_G+\Omega^{1/2}\xi)\Pi(a-1,c+1,\xi) \\ &+ \frac{k_3}{\Omega}[1-\Omega^{-1/2}\frac{\partial}{\partial\xi}+\Omega^{-1}\frac{\partial^2}{\partial\xi^2}-\cdots](\Omega\phi_G+\Omega^{1/2}\xi)(\Omega\phi_G+\Omega^{1/2}\xi-1)\Pi(a,c,\xi) \\ &- \left(\frac{k_1}{\Omega}a(\Omega\phi_G+\Omega^{1/2}\xi) + \frac{k_2}{\Omega}c(\Omega\phi_G+\Omega^{1/2}\xi)+\frac{k_3}{\Omega}(\Omega\phi_G+\Omega^{1/2}\xi)(\Omega\phi_G+\Omega^{1/2}\xi-1)\right)\Pi(a,c,\xi)\end{aligned} \tag{40}$$

For the rate constants of the system, we have $k_1, k_2 \gg k_3$. We define the following parameters

$$K_1 = \frac{k_1}{\Omega} \qquad \gamma = \Omega k_2^{-1} \tag{41}$$

Following Mastny et al. [2], we express Π as a power series in Ω^{-1},

$$\Pi(a,c,\xi) = W_0(a,c,\xi) + \Omega^{-1}W_1(a,c,\xi) + \Omega^{-2}W_2(a,c,\xi) + \cdots$$

and substitute into (40) to obtain the following expanded master equation

$$\begin{aligned}
&\Omega^{-1}\left(\frac{\partial W_0(a,c,\xi)}{\partial t} + \Omega^{-1}\frac{\partial W_1(a,c,\xi)}{\partial t} + \cdots\right) - \Omega^{-1/2}\frac{d\phi_G}{dt}\left(\frac{\partial W_0(a,c,\xi)}{\partial \xi} + \Omega^{-1}\frac{\partial W_1(a,c,\xi)}{\partial \xi} + \cdots\right) \\
&= K_1\Omega^{-1}(a+1)(\Omega\phi_G + \Omega^{1/2}\xi)\left(W_0(a+1,c-1,\xi) + \Omega^{-1}W_1(a+1,c-1,\xi) + \cdots\right) \\
&+ (\gamma\Omega)^{-1}(c+1)[1 - \Omega^{-1/2}\frac{\partial}{\partial \xi} + \Omega^{-1}\frac{\partial^2}{\partial \xi^2} - \cdots](\Omega\phi_G + \Omega^{1/2}\xi)\left(W_0(a-1,c+1,\xi) + \Omega^{-1}W_1(a-1,c+1,\xi) + \cdots\right) \\
&+ k_3\Omega^{-2}[1 - \Omega^{-1/2}\frac{\partial}{\partial \xi} + \Omega^{-1}\frac{\partial^2}{\partial \xi^2} - \cdots](\Omega\phi_G + \Omega^{1/2}\xi)(\Omega\phi_G + \Omega^{1/2}\xi - 1)\left(W_0(a,c,\xi) + \Omega^{-1}W_1(a,c,\xi) + \cdots\right) \\
&- \left(K_1\Omega^{-1}a(\Omega\phi_G + \Omega^{1/2}\xi) + \gamma^{-1}\Omega^{-1}c(\Omega\phi_G + \Omega^{1/2}\xi)\right)\left(W_0(a,c,\xi) + \Omega^{-1}W_1(a,c,\xi) + \cdots\right) \\
&- k_3\Omega^{-2}(\Omega\phi_G + \Omega^{1/2}\xi)(\Omega\phi_G + \Omega^{1/2}\xi - 1)\left(W_0(a,c,\xi) + \Omega^{-1}W_1(a,c,\xi) + \cdots\right)
\end{aligned} \tag{42}$$

Ω^0 terms. Collecting Ω^0 terms from (42) gives

$$\begin{aligned}
0 = K_1(a+1)\phi_G W_0(a+1,c-1,\xi) - \left(K_1 a\phi_G + \gamma^{-1}c\phi_G\right)W_0(a,c,\xi) \\
+ \gamma^{-1}(c+1)\phi_G W_0(a-1,c+1,\xi)
\end{aligned} \tag{43}$$

Since none of the terms multiplying joint densities in (43) contain ξ, we can integrate (43) to obtain an equation for marginal density as a function of a and c only. Also we note that because of the stoichiometry of the problem $a + c = N_0$ and we can replace c with $N_0 - a$. Making these substitutions in (43), we obtain

$$\begin{aligned}
0 = K_1(a+1)W_{0a}(a+1) - K_1 a W_{0a}(a) - \gamma^{-1}N_0 W_{0a}(a) + \gamma^{-1}a W_{0a}(a) \\
+ \gamma^{-1}N_0 W_{0a}(a-1) - \gamma^{-1}(a-1)W_{0a}(a-1)
\end{aligned} \tag{44}$$

An analytical expression for marginal density $W_{0a}(a)$ can be obtained by taking the z-transform of the equation (44). That produces equation (23) of the paper. The distribution in (23) is a binomial distribution $W_{0a} \sim \text{Bin}(\frac{q}{1+q}, N_0)$ in which $q = 1/(\gamma K_1)$. Since $a + c = N_0$ equation (24) is an immediate consequence of (23). From equation (43), it is also clear that $W_0(a,\xi) = W_{0a}(a)W_{0\xi}(\xi)$.

$\Omega^{-1/2}$ terms. Collecting $\Omega^{-1/2}$ terms from equation (42) gives

$$\begin{aligned}
-\frac{d\phi_G}{dt}\frac{\partial W_0(a,c,\xi)}{\partial \xi} =& K_1(a+1)\xi W_0(a+1,c-1,\xi) - K_1 a\xi W_0(a,c,\xi) + \gamma^{-1}(c+1)\xi W_0(a-1,c+1,\xi) \\
&- \gamma^{-1}c\xi W_0(a,c,\xi) + k_3\frac{\partial\left(\phi_G^2 W_0(a,c,\xi)\right)}{\partial \xi}
\end{aligned} \tag{45}$$

We recall that argument c in function W_0 is redundant because $a + c = N_0$ at all times. Summing equation (45) over all the values of a and c along with using the independence of a and ξ gives us

$$-\frac{d\phi_G}{dt} = -\gamma^{-1}\langle c\rangle\phi_G + k_3\phi_G^2 \tag{46}$$

which is (25) in the paper. Equations (23) and (46) together give an approximation of the populations of A, C and G when G has risen over a threshold value.

Ω^{-1} terms. Collecting Ω^{-1} terms from equation (42) gives

$$\begin{aligned}\frac{\partial W_0(a,c,\xi)}{\partial t} =& K_1(a+1)\gamma\phi_G W_1(a+1,c-1,\xi) - K_1 a\phi_G\gamma W_1(a-1,c+1,\xi)\\ &+ \frac{c+1}{\gamma}\frac{\partial}{\partial\xi}(\xi W_0(a-1,c+1,\xi)) + \frac{c+1}{2\gamma}\frac{\partial^2}{\partial\xi^2}(\phi_G W_0(a-1,c+1,\xi)\\ &- c\phi_G W_1(a,c,\xi)) + 2k_3\phi_G\frac{\partial}{\partial\xi}(\xi W_0(a,c,\xi)) + \frac{k_3}{2}\phi_G^2\frac{\partial^2}{\partial\xi^2}W_0(a,c,\xi)\end{aligned} \tag{47}$$

Summing equation (47) for all values of a and c gives

$$\frac{\partial W_{0\xi}(\xi)}{\partial t} = -\frac{\langle c\rangle}{\gamma}\frac{\partial}{\partial\xi}(\xi W_{0\xi}(\xi)) + \frac{1}{2}\frac{\langle c\rangle\phi_G}{\gamma}\frac{\partial^2}{\partial\xi^2}W_{0\xi}(\xi) + 2k_3\phi_G\frac{\partial}{\partial\xi}(\xi W_{0\xi}(\xi)) + \frac{k_3}{2}\phi_G^2\frac{\partial^2}{\partial\xi^2}W_{0\xi}(\xi) \tag{48}$$

Rearranging equation (48) gives

$$\frac{\partial W_{0\xi}(\xi)}{\partial t} = -\frac{\partial}{\partial\xi}\left[\left(\frac{\langle c\rangle}{\gamma} - 2k_3\phi_G\right)\xi W_{0\xi}(\xi)\right] + \frac{1}{2}\frac{\partial^2}{\partial\xi^2}\left[\left(\frac{\langle c\rangle\phi_G}{\gamma} + k_3\phi_G^2\right)W_{0\xi}(\xi)\right] \tag{49}$$

Equation (49) is a linear Fokker-Planck equation and is the same as equation (26) of the paper. Its equivalent stochastic differential equation is given by

$$d\xi = \left(\frac{\langle c\rangle}{\gamma} - 2k_3\phi_G\right)\xi\, dt + \sqrt{\frac{\langle c\rangle\phi_G}{\gamma} + k_3\phi_G^2}\, dW \tag{50}$$

in which dW is a normally distributed random variable with zero mean and variance dt [1]. Equation (50) here is the same as equation (27) of the paper.

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