Supporting Text2

Stable stochastic dynamics in yeast cell cycle

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The equations for the moments of states of genes, numbers of mRNA molecules, and numbers of protein molecules residing in each of chemical states are derived from the master equation. Those equations are approximated by truncating them at the 2nd order of cumulants and by neglecting the cross correlation between different molecular species. For a concrete example, equations for the moments related to the changes in the number of Clb5,6 are shown below. Equations for other 12 sets of proteins, mRNA and genes in the network can be derived in the same way.

Variables that appear in equations are the following: μ specifies the protein considered. In the present Supporting Text, $\mu =$Clb5,6. $\delta_{i,j}$ and $\delta_{R_\mu,j}$ are the Kronecker deltas. i = 1, 2, ..., or 5 denotes the stage of cell cycle at time t and R_μ = 1 or 2 represents the number of copies of the *clb*5,6 gene. R_μ increases from 1 to 2 by replication of the gene during stage1 and decreases from 2 to 1 by cytokinesis at C_5. The index α represents the gene state, α = 1 or 0 when R_μ = 1 and α is a pair of numbers, α = 11, 10, 01 or 00 when R_μ = 2. $D_\alpha^{\rm int}(\mu,t)$ is the probability that μ th gene is in the state of α. $N_{m\alpha}^{\rm int}(\mu,t)$ is the mean number of mRNA molecules of *clb*5,6 at time *t* when the *clb*5,6 gene is in the state α. $N_X^{\rm int}(\mu,t)$ is the mean number of Clb5,6 protein molecules at the chemical state *X*. We write the mean square of the number of mRNA molecules as $M_{m\alpha}^{\rm int}(\mu,t)$ and the mean square of the number of Clb5,6 protein molecules as $M_X^{\rm int}(\mu,t)$. Variances are then calculated as $\sigma_{m\alpha}^{\rm int}(\mu,t) = M_{m\alpha}^{\rm int}(\mu,t) - \left(N_{m\alpha}^{\rm int}(\mu,t)\right)^2$ and $\sigma_X^{\rm int}(\mu,t) = M_X^{\rm int}(\mu,t) - \left(N_X^{\rm int}(\mu,t)\right)^2$.

Kinetic parameters in the equations are coefficients of rates of reactions: translation (η), protein-complex formation (h_b), ubiquitination (h_u), degradation of ubiquinated protein (k_0), degradation of unubiquinated protein (k_1), degradation of mRNA (k_2), dissociation of activator from DNA (*f*), binding of activator to DNA (h_t), synthesis of mRNA from a single copy of the gene in the off state (g_0), and synthesis of mRNA from a single copy of the gene in the on state (g_1).

Since equations contain the index *i* representing the stage in cell cycle at time *t* and R_μ of the number of copies of the μth gene, the equations have different nonzero terms depending on *i*(*t*) and $R_\mu(t)$. Equations are not self-contained to determine *i*(*t*) and R_μ(t) but *i*(*t*) and R_μ(t) are changed by following the stochastic rules defined independently of the equations of moments. See the main text for the rules to change *i*(*t*) and R_μ(t). When *i* is changed at C_1, C_2, C_3, or C_4, $D_\alpha^{\rm int}(\mu,t)$, $N_{m\alpha}^{\rm int}(\mu,t)$, $N_X^{\rm int}(\mu,t)$, $M_{m\alpha}^{\rm int}(\mu,t)$, and $M_X^{\rm int}(\mu,t)$ are handed continuously to the next stage. When i is changed at C_5 (i.e., at cytokinesis) from i = 4 at time t to i = 5 at time t+Δt, $D_{\alpha}^{\text{int}}(\mu,t)$ is determined to be $D_{\xi}^{\text{int}}(\mu,t+\Delta t)=D_{\xi 1}^{\text{int}}(\mu,t)+D_{\xi 0}^{\text{int}}(\mu,t)$ and $N_{m\alpha}^{\text{int}}(\mu,t)$ and $N_{X}^{\text{int}}(\mu,t)$ are stochastically reduced roughly half as described in the main text. $M_{m\alpha}^{\text{int}}(\mu,t)$ and $M_{X}^{\text{int}}(\mu,t)$ are handed to make $F_{m\alpha}^{\text{int}}(\mu,t)$ and $F_{X}^{\text{int}}(\mu,t)$ continuous at C_5. When R_{μ} is increased on replication of the μth gene from R_{μ} = 1 at time t to R_{μ} = 2 at time t+Δt, $D_{\alpha}^{\text{int}}(\mu,t)$, $N_{m\alpha}^{\text{int}}(\mu,t)$ and $M_{m\alpha}^{\text{int}}(\mu,t)$ are determined as $D_{\xi\xi'}^{\text{int}}(\mu,t+\Delta t)=D_{\xi}^{\text{int}}(\mu,t)\cdot D_{\xi'}^{\text{int}}(\mu,t)$, $N_{m\xi\xi'}^{\text{int}}(\mu,t+\Delta t)=N_{m\xi}^{\text{int}}(\mu,t)+N_{m\xi'}^{\text{int}}(\mu,t)$, and $M_{m\xi\xi'}^{\text{int}}(\mu,t+\Delta t)=2\left(M_{m\xi}^{\text{int}}(\mu,t)+N_{m\xi}^{\text{int}}(\mu,t)\cdot N_{m\xi'}^{\text{int}}(\mu,t)\right)$, which ensures continuity of $F_{m\alpha}^{\text{int}}(\mu,t)$. $N_{X}^{\text{int}}(\mu,t)$ and $M_{m\alpha}^{\text{int}}(\mu,t)$ are $N_{X}^{\text{int}}(\mu,t+\Delta t)=N_{X}^{\text{int}}(\mu,t)$ and $M_{X}^{\text{int}}(\mu,t+\Delta t)=M_{X}^{\text{int}}(\mu,t)$. Duration of each stage, timing of replication of each gene and the ratio of distribution of molecules at cytokinesis are fluctuating at every cycle as described in the main text, and thus these cycle-by-cycle variations are the origins of extrinsic fluctuations in the present model.

< Equations for the numbers of protein molecules >

$$\frac{d}{dt}N_{(1u)}^{\mathrm{int}}(\mu,t)=\eta\cdot\left(\delta_{R_\mu,1}\sum_{\alpha=1\text{ or }0}D_\alpha^{\mathrm{int}}(\mu,t)N_{m\alpha}^{\mathrm{int}}(\mu,t)+\delta_{R_\mu,2}\sum_{\alpha=11,10,01,\text{ or }00}D_\alpha^{\mathrm{int}}(\mu,t)N_{m\alpha}^{\mathrm{int}}(\mu,t)\right)$$
$$-\left\{k_1+h_b\sum_X N_X^{\mathrm{int}}(Sic1,t)+(\delta_{i,3}+\delta_{i,4}+\delta_{i,5})h_u\left(N_{(1u)(1p)}^{\mathrm{int}}(Cdc20,t)+N_{(0u)(1p)}^{\mathrm{int}}(Cdc20,t)\right)\right\}N_{(1u)}^{\mathrm{int}}(\mu,t)$$

$$\frac{d}{dt}N_{(0u)}^{\mathrm{int}}(\mu,t)=-\left(k_0+h_b\sum_X N_X^{\mathrm{int}}(Sic1,t)\right)N_{(0u)}^{\mathrm{int}}(\mu,t)+(\delta_{i,3}+\delta_{i,4}+\delta_{i,5})h_u\left(N_{(1u)(1p)}^{\mathrm{int}}(Cdc20,t)+N_{(0u)(1p)}^{\mathrm{int}}(Cdc20,t)\right)N_{(1u)}^{\mathrm{int}}(\mu,t)$$

$$\frac{d}{dt}M_{(1u)}^{\mathrm{int}}(\mu,t)=\eta\cdot\left(\delta_{R_\mu,1}\sum_{\alpha=1\text{ or }0}D_\alpha^{\mathrm{int}}(\mu,t)N_{m\alpha}^{\mathrm{int}}(\mu,t)+\delta_{R_\mu,2}\sum_{\alpha=11,10,01,\text{ or }00}D_\alpha^{\mathrm{int}}(\mu,t)N_{m\alpha}^{\mathrm{int}}(\mu,t)\right)\left(2N_{(1u)}^{\mathrm{int}}(\mu,t)+1\right)$$
$$-\left\{k_1+h_b\sum_X N_X^{\mathrm{int}}(Sic1,t)+(\delta_{i,3}+\delta_{i,4}+\delta_{i,5})h_u\left(N_{(1u)(1p)}^{\mathrm{int}}(Cdc20,t)+N_{(0u)(1p)}^{\mathrm{int}}(Cdc20,t)\right)\right\}\left(2M_{(1u)}^{\mathrm{int}}(\mu,t)-N_{(1u)}^{\mathrm{int}}(\mu,t)\right)$$

$$\frac{d}{dt}M_{(0u)}^{\mathrm{int}}(\mu,t)=-\left(k_0+h_b\sum_X N_X^{\mathrm{int}}(Sic1,t)\right)\left(2M_{(0u)}^{\mathrm{int}}(\mu,t)-N_{(0u)}^{\mathrm{int}}(\mu,t)\right)$$
$$+(\delta_{i,3}+\delta_{i,4}+\delta_{i,5})h_u\left(N_{(1u)(1p)}^{\mathrm{int}}(Cdc20,t)+N_{(0u)(1p)}^{\mathrm{int}}(Cdc20,t)\right)N_{(1u)}^{\mathrm{int}}(\mu,t)\left(2N_{(0u)}^{\mathrm{int}}(\mu,t)+1\right)$$

< Equations for the state of gene and the number of mRNA molecules <u>before replication of the μth gene</u> >

$$\frac{d}{dt}D_1^{\mathrm{int}}(\mu,t)=\delta_{R_\mu,1}\left[-f\,D_1^{\mathrm{int}}(\mu,t)+h_t\left(M_{(1p)(1p)}^{\mathrm{int}}(MBF,t)-N_{(1p)(1p)}^{\mathrm{int}}(MBF,t)\right)D_0^{\mathrm{int}}(\mu,t)\right]$$

$$\frac{d}{dt}D_0^{\mathrm{int}}(\mu,t)=\delta_{R_\mu,1}\left[f\,D_1^{\mathrm{int}}(\mu,t)-h_t\left(M_{(1p)(1p)}^{\mathrm{int}}(MBF,t)-N_{(1p)(1p)}^{\mathrm{int}}(MBF,t)\right)D_0^{\mathrm{int}}(\mu,t)\right]$$

$$\frac{d}{dt}D_1^{\mathrm{int}}(\mu,t)N_{m1}^{\mathrm{int}}(\mu,t)=\delta_{R_\mu,1}\left[D_1^{\mathrm{int}}(\mu,t)\left\{g_1-(k_2+f)N_{m1}^{\mathrm{int}}(\mu,t)\right\}+h_t\left(M_{(1p)(1p)}^{\mathrm{int}}(MBF,t)-N_{(1p)(1p)}^{\mathrm{int}}(MBF,t)\right)D_0^{\mathrm{int}}(\mu,t)N_{m0}^{\mathrm{int}}(\mu,t)\right]$$

$$\frac{d}{dt}D_0^{\mathrm{int}}(\mu,t)N_{m0}^{\mathrm{int}}(\mu,t)=\delta_{R_\mu,1}\left[D_0^{\mathrm{int}}(\mu,t)\left\{g_0-\left(k_2+h_t\left(M_{(1p)(1p)}^{\mathrm{int}}(MBF,t)-N_{(1p)(1p)}^{\mathrm{int}}(MBF,t)\right)\right)N_{m0}^{\mathrm{int}}(\mu,t)\right\}+f\,D_1^{\mathrm{int}}(\mu,t)N_{m1}^{\mathrm{int}}(\mu,t)\right]$$

$$\begin{aligned}\frac{d}{dt}D_1^{\mathrm{int}}(\mu,t)M_{m1}^{\mathrm{int}}(\mu,t)=\delta_{R_\mu,1}\Big[&D_1^{\mathrm{int}}(\mu,t)\left\{g_1\left(2N_{m1}^{\mathrm{int}}(\mu,t)+1\right)-k_2\left(2M_{m1}^{\mathrm{int}}(\mu,t)-N_{m1}^{\mathrm{int}}(\mu,t)\right)-f\,M_{m1}^{\mathrm{int}}(\mu,t)\right\}\\&+h_t\left(M_{(1p)(1p)}^{\mathrm{int}}(MBF,t)-N_{(1p)(1p)}^{\mathrm{int}}(MBF,t)\right)D_0^{\mathrm{int}}(\mu,t)M_{m0}^{\mathrm{int}}(\mu,t)\Big]\end{aligned}$$

$$\begin{aligned}\frac{d}{dt}D_0^{\mathrm{int}}(\mu,t)M_{m0}^{\mathrm{int}}(\mu,t)=\delta_{R_\mu,1}\Big[&D_0^{\mathrm{int}}(\mu,t)\left\{g_0\left(2N_{m0}^{\mathrm{int}}(\mu,t)+1\right)-k_2\left(2M_{m0}^{\mathrm{int}}(\mu,t)-N_{m0}^{\mathrm{int}}(\mu,t)\right)-h_t\left(M_{(1p)(1p)}^{\mathrm{int}}(MBF,t)-N_{(1p)(1p)}^{\mathrm{int}}(MBF,t)\right)M_{m0}^{\mathrm{int}}(\mu,t)\right\}\\&+f\,D_1^{\mathrm{int}}(\mu,t)M_{m1}^{\mathrm{int}}(\mu,t)\Big]\end{aligned}$$

< Equations for the state of gene and the number of mRNA molecules after replication of the μth gene >

$$\frac{d}{dt}D_{11}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\left[h_t\left(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\right)\left(D_{10}^{\text{int}}(\mu,t)+D_{01}^{\text{int}}(\mu,t)\right)-2f\,D_{11}^{\text{int}}(\mu,t)\right]$$

$$\frac{d}{dt}D_{10}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\left[h_t\left(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\right)\left(D_{00}^{\text{int}}(\mu,t)-D_{10}^{\text{int}}(\mu,t)\right)+f\left(D_{11}^{\text{int}}(\mu,t)-D_{10}^{\text{int}}(\mu,t)\right)\right]$$

$$\frac{d}{dt}D_{01}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\left[h_t\left(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\right)\left(D_{00}^{\text{int}}(\mu,t)-D_{01}^{\text{int}}(\mu,t)\right)+f\left(D_{11}^{\text{int}}(\mu,t)-D_{01}^{\text{int}}(\mu,t)\right)\right]$$

$$\frac{d}{dt}D_{00}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\left[-2h_t\left(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\right)D_{00}^{\text{int}}(\mu,t)+f\left(D_{10}^{\text{int}}(\mu,t)+D_{01}^{\text{int}}(\mu,t)\right)\right]$$

$$\begin{aligned}\frac{d}{dt}D_{11}^{\text{int}}(\mu,t)N_{m11}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\Big[&D_{11}^{\text{int}}(\mu,t)\left(2g_1-k_2N_{m11}^{\text{int}}(\mu,t)\right)-2f\,D_{11}^{\text{int}}(\mu,t)N_{m11}^{\text{int}}(\mu,t)\\&+h_t\left(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\right)\left(D_{10}^{\text{int}}(\mu,t)N_{m10}^{\text{int}}(\mu,t)+D_{01}^{\text{int}}(\mu,t)N_{m01}^{\text{int}}(\mu,t)\right)\Big]\end{aligned}$$

$$\begin{aligned}\frac{d}{dt}D_{10}^{\text{int}}(\mu,t)N_{m10}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\Big[&D_{10}^{\text{int}}(\mu,t)\left(g_1+g_0-k_2N_{m10}^{\text{int}}(\mu,t)\right)+f\left(D_{11}^{\text{int}}(\mu,t)N_{m11}^{\text{int}}(\mu,t)-D_{10}^{\text{int}}(\mu,t)N_{m10}^{\text{int}}(\mu,t)\right)\\&+h_t\left(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\right)\left(D_{00}^{\text{int}}(\mu,t)N_{m00}^{\text{int}}(\mu,t)-D_{10}^{\text{int}}(\mu,t)N_{m10}^{\text{int}}(\mu,t)\right)\Big]\end{aligned}$$

$$\begin{aligned}\frac{d}{dt}D_{01}^{\text{int}}(\mu,t)N_{m01}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\Big[&D_{01}^{\text{int}}(\mu,t)\left(g_1+g_0-k_2N_{m01}^{\text{int}}(\mu,t)\right)+f\left(D_{11}^{\text{int}}(\mu,t)N_{m11}^{\text{int}}(\mu,t)-D_{01}^{\text{int}}(\mu,t)N_{m01}^{\text{int}}(\mu,t)\right)\\&+h_t\left(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\right)\left(D_{00}^{\text{int}}(\mu,t)N_{m00}^{\text{int}}(\mu,t)-D_{01}^{\text{int}}(\mu,t)N_{m01}^{\text{int}}(\mu,t)\right)\Big]\end{aligned}$$

$$\frac{d}{dt}D_{00}^{\text{int}}(\mu,t)N_{m00}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\Big[D_{00}^{\text{int}}(\mu,t)\Big(2g_0-k_2N_{m00}^{\text{int}}(\mu,t)\Big)+f\Big(D_{10}^{\text{int}}(\mu,t)N_{m10}^{\text{int}}(\mu,t)+D_{01}^{\text{int}}(\mu,t)N_{m01}^{\text{int}}(\mu,t)\Big)$$
$$-2h_t\Big(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\Big)D_{00}^{\text{int}}(\mu,t)N_{m00}^{\text{int}}(\mu,t)\Big]$$

$$\frac{d}{dt}D_{11}^{\text{int}}(\mu,t)M_{m11}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\Big[D_{11}^{\text{int}}(\mu,t)\Big\{2g_1\Big(2N_{m11}^{\text{int}}(\mu,t)+1\Big)-k_2\Big(2M_{m11}^{\text{int}}(\mu,t)-N_{m11}^{\text{int}}(\mu,t)\Big)\Big\}-2f\,D_{11}^{\text{int}}(\mu,t)M_{m11}^{\text{int}}(\mu,t)$$
$$+h_t\Big(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\Big)\Big(D_{10}^{\text{int}}(\mu,t)M_{m10}^{\text{int}}(\mu,t)+D_{01}^{\text{int}}(\mu,t)M_{m01}^{\text{int}}(\mu,t)\Big)\Big]$$

$$\frac{d}{dt}D_{10}^{\text{int}}(\mu,t)M_{m10}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\Big[D_{10}^{\text{int}}(\mu,t)\Big\{(g_1+g_0)\Big(2N_{m10}^{\text{int}}(\mu,t)+1\Big)-k_2\Big(2M_{m10}^{\text{int}}(\mu,t)-N_{m10}^{\text{int}}(\mu,t)\Big)\Big\}+f\Big(D_{11}^{\text{int}}(\mu,t)M_{m11}^{\text{int}}(\mu,t)-D_{10}^{\text{int}}(\mu,t)M_{m10}^{\text{int}}(\mu,t)\Big)$$
$$+h_t\Big(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\Big)\Big(D_{00}^{\text{int}}(\mu,t)M_{m00}^{\text{int}}(\mu,t)-D_{10}^{\text{int}}(\mu,t)M_{m10}^{\text{int}}(\mu,t)\Big)\Big]$$

$$\frac{d}{dt}D_{01}^{\text{int}}(\mu,t)M_{m01}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\Big[D_{01}^{\text{int}}(\mu,t)\Big\{(g_1+g_0)\Big(2N_{m01}^{\text{int}}(\mu,t)+1\Big)-k_2\Big(2M_{m01}^{\text{int}}(\mu,t)-N_{m01}^{\text{int}}(\mu,t)\Big)\Big\}+f\Big(D_{11}^{\text{int}}(\mu,t)M_{m11}^{\text{int}}(\mu,t)-D_{01}^{\text{int}}(\mu,t)M_{m01}^{\text{int}}(\mu,t)\Big)$$
$$+h_t\Big(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\Big)\Big(D_{00}^{\text{int}}(\mu,t)M_{m00}^{\text{int}}(\mu,t)-D_{01}^{\text{int}}(\mu,t)M_{m01}^{\text{int}}(\mu,t)\Big)\Big]$$

$$\frac{d}{dt}D_{00}^{\text{int}}(\mu,t)M_{m00}^{\text{int}}(\mu,t)=\delta_{R_\mu,2}\Big[D_{00}^{\text{int}}(\mu,t)\Big\{2g_0\Big(2N_{m00}^{\text{int}}(\mu,t)+1\Big)-k_2\Big(2M_{m00}^{\text{int}}(\mu,t)-N_{m00}^{\text{int}}(\mu,t)\Big)\Big\}+f\Big(D_{10}^{\text{int}}(\mu,t)M_{m10}^{\text{int}}(\mu,t)+D_{01}^{\text{int}}(\mu,t)M_{m01}^{\text{int}}(\mu,t)\Big)$$
$$-2h_t\Big(M_{(1p)(1p)}^{\text{int}}(MBF,t)-N_{(1p)(1p)}^{\text{int}}(MBF,t)\Big)D_{00}^{\text{int}}(\mu,t)M_{m00}^{\text{int}}(\mu,t)\Big]$$