Supporting Material

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MASTER EQUATIONS

16 Master equations for the dual-feedback network with two genes mutually repress and activate each other with self activation and self repression, as shown in Fig. 1(a) (main text), are given as following:

$$\begin{aligned}\frac{dP_{1111}(n_A,n_R)}{dt} &= \\ -\frac{h_{AA}}{2!}[n_A(n_A-1)]P_{1111}(n_A,n_R) &+ f_{AA}P_{0111}(n_A-2,n_R) \\ -\frac{h_{AR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{1111}(n_A,n_R) &+ f_{AR}P_{1011}(n_A,n_R-4) \\ -\frac{h_{RA}}{2!}[n_A(n_A-1)]P_{1111}(n_A,n_R) &+ f_{RA}P_{1101}(n_A-2,n_R) \\ -\frac{h_{RR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{1111}(n_A,n_R) &+ f_{RR}P_{1110}(n_A,n_R-4) \\ +k_A[(n_A+1)P_{1111}(n_A+1,n_R) &- n_AP_{1111}(n_A,n_R)] \\ +k_R[(n_R+1)P_{1111}(n_A,n_R+1) &- n_RP_{1111}(n_A,n_R)] \\ +g_A^{11}[P_{1111}(n_A-1,n_R) &- P_{1111}(n_A,n_R)] \\ +g_R^{11}[P_{1111}(n_A,n_R-1) &- P_{1111}(n_A,n_R)]\end{aligned} \tag{1}$$

$$\begin{aligned}\frac{dP_{1011}(n_A,n_R)}{dt} &= \\ -\frac{h_{AA}}{2!}[n_A(n_A-1)]P_{1011}(n_A,n_R) &+ f_{AA}P_{0011}(n_A-2,n_R) \\ +\frac{h_{AR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{1111}(n_A,n_R+4) &- f_{AR}P_{1011}(n_A,n_R) \\ -\frac{h_{RA}}{2!}[n_A(n_A-1)]P_{1011}(n_A,n_R) &+ f_{RA}P_{1001}(n_A-2,n_R) \\ -\frac{h_{RR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{1011}(n_A,n_R) &+ f_{RR}P_{1010}(n_A,n_R-4) \\ +k_A[(n_A+1)P_{1011}(n_A+1,n_R) &- n_AP_{1011}(n_A,n_R)] \\ +k_R[(n_R+1)P_{1011}(n_A,n_R+1) &- n_RP_{1011}(n_A,n_R)] \\ +g_A^{10}[P_{1011}(n_A-1,n_R) &- P_{1011}(n_A,n_R)] \\ +g_R^{11}[P_{1011}(n_A,n_R-1) &- P_{1011}(n_A,n_R)]\end{aligned} \tag{2}$$

$$
\begin{aligned}
\frac{dP_{0111}(n_A,n_R)}{dt} &= \\
+\frac{h_{AA}}{2!}[(n_A+2)(n_A+1)]P_{1111}(n_A+2,n_R) - f_{AA}P_{0111}(n_A,n_R) \\
-\frac{h_{AR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{0111}(n_A,n_R) + f_{AR}P_{0011}(n_A,n_R-4) \\
-\frac{h_{RA}}{2}[n_A(n_A-1)]P_{0111}(n_A,n_R) + f_{RA}P_{0101}(n_A-2,n_R) \\
-\frac{h_{RR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{0111}(n_A,n_R) + f_{RR}P_{0110}(n_A,n_R-4) \\
+k_A[(n_A+1)P_{0111}(n_A+1,n_R) - n_AP_{0111}(n_A,n_R)] \\
+k_R[(n_R+1)P_{0111}(n_A,n_R+1) - n_RP_{0111}(n_A,n_R)] \\
+g_A^{01}[P_{0111}(n_A-1,n_R) - P_{0111}(n_A,n_R)] \\
+g_R^{11}[P_{0111}(n_A,n_R-1) - P_{0111}(n_A,n_R)]
\end{aligned} \tag{3}
$$

$$
\begin{aligned}
\frac{dP_{0011}(n_A,n_R)}{dt} &= \\
+\frac{h_{AA}}{2!}[(n_A+2)(n_A+1)]P_{1011}(n_A+2,n_R) - f_{AA}P_{0011}(n_A,n_R) \\
+\frac{h_{AR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{0111}(n_A,n_R+4) - f_{AR}P_{0011}(n_A,n_R) \\
-\frac{h_{RA}}{2!}[n_A(n_A-1)]P_{0011}(n_A,n_R) + f_{RA}P_{0001}(n_A-2,n_R) \\
-\frac{h_{RR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{0011}(n_A,n_R) + f_{RR}P_{0010}(n_A,n_R-4) \\
+k_A[(n_A+1)P_{0011}(n_A+1,n_R) - n_AP_{0011}(n_A,n_R)] \\
+k_R[(n_R+1)P_{0011}(n_A,n_R+1) - n_RP_{0011}(n_A,n_R)] \\
+g_A^{00}[P_{0011}(n_A-1,n_R) - P_{0011}(n_A,n_R)] \\
+g_R^{11}[P_{0011}(n_A,n_R-1) - P_{0011}(n_A,n_R)]
\end{aligned} \tag{4}
$$

$$
\begin{aligned}
&\frac{dP_{1110}(n_A,n_R)}{dt} = \\
&-\frac{h_{AA}}{2!}[n_A(n_A-1)]P_{1110}(n_A,n_R) + f_{AA}P_{0110}(n_A-2,n_R) \\
&-\frac{h_{AR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{1110}(n_A,n_R) + f_{AR}P_{1010}(n_A,n_R-4) \\
&-\frac{h_{RA}}{2!}[n_A(n_A-1)]P_{1110}(n_A,n_R) + f_{RA}P_{1100}(n_A-2,n_R) \\
&+\frac{h_{RR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{1111}(n_A,n_R+2) - f_{RR}P_{1110}(n_A,n_R) \\
&+k_A[(n_A+1)P_{1110}(n_A+1,n_R) - n_AP_{1110}(n_A,n_R)] \\
&+k_R[(n_R+1)P_{1110}(n_A,n_R+1) - n_RP_{1110}(n_A,n_R)] \\
&+g_A^{11}[P_{1110}(n_A-1,n_R) - P_{1110}(n_A,n_R)] \\
&+g_R^{10}[P_{1110}(n_A,n_R-1) - P_{1110}(n_A,n_R)] \qquad (5)
\end{aligned}
$$

$$
\begin{aligned}
&\frac{dP_{1010}(n_A,n_R)}{dt} = \\
&-\frac{h_{AA}}{2!}[n_A(n_A-1)]P_{1010}(n_A,n_R) + f_{AA}P_{0010}(n_A-2,n_R) \\
&+\frac{h_{AR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{1110}(n_A,n_R+4) - f_{AR}P_{1010}(n_A,n_R) \\
&-\frac{h_{RA}}{2!}[n_A(n_A-1)]P_{1010}(n_A,n_R) + f_{RA}P_{1000}(n_A-2,n_R) \\
&+\frac{h_{RR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{1011}(n_A,n_R+4) - f_{RR}P_{1010}(n_A,n_R) \\
&+k_A[(n_A+1)P_{1010}(n_A+1,n_R) - n_AP_{1010}(n_A,n_R)] \\
&+k_R[(n_R+1)P_{1010}(n_A,n_R+1) - n_RP_{1010}(n_A,n_R)] \\
&+g_A^{10}[P_{1010}(n_A-1,n_R) - P_{1010}(n_A,n_R)] \\
&+g_R^{10}[P_{1010}(n_A,n_R-1) - P_{1010}(n_A,n_R)] \qquad (6)
\end{aligned}
$$

$$
\begin{aligned}
&\frac{dP_{0110}(n_A,n_R)}{dt} = \\
&+\frac{h_{AA}}{2!}[(n_A+2)(n_A+1)]P_{1110}(n_A+2,n_R) - f_{AA}P_{0110}(n_A,n_R) \\
&-\frac{h_{AR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{0110}(n_A,n_R) + f_{AR}P_{0010}(n_A,n_R-4) \\
&-\frac{h_{RA}}{2!}[n_A(n_A-1)]P_{0110}(n_A,n_R) + f_{RA}P_{0100}(n_A-2,n_R) \\
&+\frac{h_{RR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{0111}(n_A,n_R+4) - f_{RR}P_{0110}(n_A,n_R) \\
&+k_A[(n_A+1)P_{0110}(n_A+1,n_R) - n_AP_{0110}(n_A,n_R)] \\
&+k_R[(n_R+1)P_{0110}(n_A,n_R+1) - n_RP_{0110}(n_A,n_R)] \\
&+g_A^{01}[P_{0110}(n_A-1,n_R) - P_{0110}(n_A,n_R)] \\
&+g_R^{10}[P_{0110}(n_A,n_R-1) - P_{0110}(n_A,n_R)] \qquad (7)
\end{aligned}
$$

$$
\begin{aligned}
&\frac{dP_{0010}(n_A,n_R)}{dt} = \\
&+\frac{h_{AA}}{2!}[(n_A+2)(n_A+1)]P_{1010}(n_A+2,n_R) - f_{AA}P_{0010}(n_A,n_R) \\
&+\frac{h_{AR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{0110}(n_A,n_R+2) - f_{AR}P_{0010}(n_A,n_R) \\
&-\frac{h_{RA}}{2!}[n_A(n_A-1)]P_{0010}(n_A,n_R) + f_{RA}P_{0000}(n_A-2,n_R) \\
&+\frac{h_{RR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{0011}(n_A,n_R+2) - f_{RR}P_{0010}(n_A,n_R) \\
&+k_A[(n_A+1)P_{0010}(n_A+1,n_R) - n_AP_{0010}(n_A,n_R)] \\
&+k_R[(n_R+1)P_{0010}(n_A,n_R+1) - n_RP_{0010}(n_A,n_R)] \\
&+g_A^{00}[P_{0010}(n_A-1,n_R) - P_{0010}(n_A,n_R)] \\
&+g_R^{10}[P_{0010}(n_A,n_R-1) - P_{0010}(n_A,n_R)] \qquad (8)
\end{aligned}
$$

$$
\begin{aligned}
\frac{dP_{1101}(n_A,n_R)}{dt} &= \\
-\frac{h_{AA}}{2!}[n_A(n_A-1)]P_{1101}(n_A,n_R) + f_{AA}P_{0101}(n_A-2,n_R) \\
-\frac{h_{AR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{1101}(n_A,n_R) + f_{AR}P_{1001}(n_A,n_R-4) \\
+\frac{h_{RA}}{2!}[(n_A+2)(n_A+1)]P_{1111}(n_A+2,n_R) - f_{RA}P_{1101}(n_A,n_R) \\
-\frac{h_{RR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{1101}(n_A,n_R) + f_{RR}P_{1100}(n_A,n_R-4) \\
+k_A[(n_A+1)P_{1101}(n_A+1,n_R) - n_AP_{1101}(n_A,n_R)] \\
+k_R[(n_R+1)P_{1101}(n_A,n_R+1) - n_RP_{1101}(n_A,n_R)] \\
+g_A^{11}[P_{1101}(n_A-1,n_R) - P_{1101}(n_A,n_R)] \\
+g_R^{01}[P_{1101}(n_A,n_R-1) - P_{1101}(n_A,n_R)] \qquad (9)
\end{aligned}
$$

$$
\begin{aligned}
\frac{dP_{1001}(n_A,n_R)}{dt} &= \\
-\frac{h_{AA}}{2!}[n_A(n_A-1)]P_{1001}(n_A,n_R) + f_{AA}P_{0001}(n_A-2,n_R) \\
+\frac{h_{AR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{1101}(n_A,n_R+4) - f_{AR}P_{1001}(n_A,n_R) \\
+\frac{h_{RA}}{2!}[(n_A+2)(n_A+1)]P_{1011}(n_A+2,n_R) - f_{RA}P_{1001}(n_A,n_R) \\
-\frac{h_{RR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{1001}(n_A,n_R) + f_{RR}P_{1000}(n_A,n_R-4) \\
+k_A[(n_A+1)P_{1001}(n_A+1,n_R) - n_AP_{1001}(n_A,n_R)] \\
+k_R[(n_R+1)P_{1001}(n_A,n_R+1) - n_RP_{1001}(n_A,n_R)] \\
+g_A^{10}[P_{1001}(n_A-1,n_R) - P_{1001}(n_A,n_R)] \\
+g_R^{01}[P_{1001}(n_A,n_R-1) - P_{1001}(n_A,n_R)] \qquad (10)
\end{aligned}
$$

$$
\begin{aligned}
\frac{dP_{0101}(n_A, n_R)}{dt} &= \\
+\frac{h_{AA}}{2!}[(n_A+2)(n_A+1)]P_{1101}(n_A+2, n_R) &- f_{AA}P_{0101}(n_A, n_R) \\
-\frac{h_{AR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{0101}(n_A, n_R) &+ f_{AR}P_{0001}(n_A, n_R-4) \\
+\frac{h_{RA}}{2!}[(n_A+2)(n_A+1)]P_{0111}(n_A+2, n_R) &- f_{RA}P_{0101}(n_A, n_R) \\
-\frac{h_{RR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{0101}(n_A, n_R) &+ f_{RR}P_{0100}(n_A, n_R-4) \\
+k_A[(n_A+1)P_{0101}(n_A+1, n_R) &- n_AP_{0101}(n_A, n_R)] \\
+k_R[(n_R+1)P_{0101}(n_A, n_R+1) &- n_RP_{0101}(n_A, n_R)] \\
+g_A^{01}[P_{0101}(n_A-1, n_R) &- P_{0101}(n_A, n_R)] \\
+g_R^{01}[P_{0101}(n_A, n_R-1) &- P_{0101}(n_A, n_R)] \qquad (11)
\end{aligned}
$$

$$
\begin{aligned}
\frac{dP_{0001}(n_A, n_R)}{dt} &= \\
+\frac{h_{AA}}{2!}[(n_A+2)(n_A+1)]P_{1001}(n_A+2, n_R) &- f_{AA}P_{0001}(n_A, n_R) \\
+\frac{h_{AR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{0101}(n_A, n_R+4) &- f_{AR}P_{0001}(n_A, n_R) \\
+\frac{h_{RA}}{2!}[(n_A+2)(n_A+1)]P_{0011}(n_A+2, n_R) &- f_{RA}P_{0001}(n_A, n_R) \\
-\frac{h_{RR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{0001}(n_A, n_R) &+ f_{RR}P_{0000}(n_A, n_R-4) \\
+k_A[(n_A+1)P_{0001}(n_A+1, n_R) &- n_AP_{0001}(n_A, n_R)] \\
+k_R[(n_R+1)P_{0001}(n_A, n_R+1) &- n_RP_{0001}(n_A, n_R)] \\
+g_A^{00}[P_{0001}(n_A-1, n_R) &- P_{0001}(n_A, n_R)] \\
+g_R^{01}[P_{0001}(n_A, n_R-1) &- P_{0001}(n_A, n_R)] \qquad (12)
\end{aligned}
$$

$$\frac{dP_{1100}(n_A, n_R)}{dt} =$$

$$-\frac{h_{AA}}{2!}[n_A(n_A-1)]P_{1100}(n_A, n_R) + f_{AA}P_{0100}(n_A-2, n_R)$$
$$-\frac{h_{AR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{1100}(n_A, n_R) + f_{AR}P_{1000}(n_A, n_R-4)$$
$$+\frac{h_{RA}}{2!}[(n_A+2)(n_A+1)]P_{1110}(n_A+2, n_R) - f_{RA}P_{1100}(n_A, n_R)$$
$$+\frac{h_{RR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{1101}(n_A, n_R+4) - f_{RR}P_{1100}(n_A, n_R)$$
$$+k_A[(n_A+1)P_{1100}(n_A+1, n_R) - n_AP_{1100}(n_A, n_R)]$$
$$+k_R[(n_R+1)P_{1100}(n_A, n_R+1) - n_RP_{1100}(n_A, n_R)]$$
$$+g_A^{11}[P_{1100}(n_A-1, n_R) - P_{1100}(n_A, n_R)]$$
$$+g_R^{00}[P_{1100}(n_A, n_R-1) - P_{1100}(n_A, n_R)] \quad (13)$$

$$\frac{dP_{1000}(n_A, n_R)}{dt} =$$

$$-\frac{h_{AA}}{2!}[n_A(n_A-1)]P_{1000}(n_A, n_R) + f_{AA}P_{0000}(n_A-2, n_R)$$
$$+\frac{h_{AR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{1100}(n_A, n_R+4) - f_{AR}P_{1000}(n_A, n_R)$$
$$+\frac{h_{RA}}{2!}[(n_A+2)(n_A+1)]P_{1010}(n_A+2, n_R) - f_{RA}P_{1000}(n_A, n_R)$$
$$+\frac{h_{RR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{1001}(n_A, n_R+4) - f_{RR}P_{1000}(n_A, n_R)$$
$$+k_A[(n_A+1)P_{1000}(n_A+1, n_R) - n_AP_{1000}(n_A, n_R)]$$
$$+k_R[(n_R+1)P_{1000}(n_A, n_R+1) - n_RP_{1000}(n_A, n_R)]$$
$$+g_A^{10}[P_{1000}(n_A-1, n_R) - P_{1000}(n_A, n_R)]$$
$$+g_R^{00}[P_{1000}(n_A, n_R-1) - P_{1000}(n_A, n_R)] \quad (14)$$

$$
\begin{aligned}
\frac{dP_{0100}(n_A,n_R)}{dt} &= \\
+\frac{h_{AA}}{2!}[(n_A+2)(n_A+1)]P_{1100}(n_A+2,n_R) - f_{AA}P_{0100}(n_A,n_R) \\
-\frac{h_{AR}}{4!}[n_R(n_R-1)(n_R-2)(n_R-3)]P_{0100}(n_A,n_R) + f_{AR}P_{0000}(n_A,n_R-4) \\
+\frac{h_{RA}}{2!}[(n_A+2)(n_A+1)]P_{0110}(n_A+2,n_R) - f_{RA}P_{0100}(n_A,n_R) \\
+\frac{h_{RR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{0101}(n_A,n_R+4) - f_{RR}P_{0100}(n_A,n_R) \\
+k_A[(n_A+1)P_{0100}(n_A+1,n_R) - n_AP_{0100}(n_A,n_R)] \\
+k_R[(n_R+1)P_{0100}(n_A,n_R+1) - n_RP_{0100}(n_A,n_R)] \\
+g_A^{01}[P_{0100}(n_A-1,n_R) - P_{0100}(n_A,n_R)] \\
+g_R^{00}[P_{0100}(n_A,n_R-1) - P_{0100}(n_A,n_R)] \quad (15)
\end{aligned}
$$

$$
\begin{aligned}
\frac{dP_{0000}(n_A,n_R)}{dt} &= \\
+\frac{h_{AA}}{2!}[(n_A+2)(n_A+1)]P_{1000}(n_A+2,n_R) - f_{AA}P_{0000}(n_A,n_R) \\
+\frac{h_{AR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{0100}(n_A,n_R+4) - f_{AR}P_{0000}(n_A,n_R) \\
+\frac{h_{RA}}{2!}[(n_A+2)(n_A+1)]P_{0010}(n_A+2,n_R) - f_{RA}P_{0000}(n_A,n_R) \\
+\frac{h_{RR}}{4!}[(n_R+4)(n_R+3)(n_R+2)(n_R+1)]P_{0001}(n_A,n_R+4) - f_{RR}P_{0000}(n_A,n_R) \\
+k_A[(n_A+1)P_{0000}(n_A+1,n_R) - n_AP_{0000}(n_A,n_R)] \\
+k_R[(n_R+1)P_{0000}(n_A,n_R+1) - n_RP_{0000}(n_A,n_R)] \\
+g_A^{00}[P_{0000}(n_A-1,n_R) - P_{0000}(n_A,n_R)] \\
+g_R^{00}[P_{0000}(n_A,n_R-1) - P_{0000}(n_A,n_R)] \quad (16)
\end{aligned}
$$

For the network circuit of the single loop negative feedback with one intermediate step, as shown in Fig. 1 (b) (main text), the master equations can be same as equ. (1) $\sim$ (16), if we set $g_A^{01} = g_A^{11}$, $g_A^{00} = g_A^{10}$, $g_R^{01} = g_R^{00}$, $g_R^{11} = g_R^{10}$.

MOMENT EQUATIONS

The m^{th} moment is defined as: $\langle n^m \rangle_\gamma = \sum_n n^m P_\gamma(n)$, where γ indicate the general gene state: 1111, 1100, etc. To get m^{th} order moment equations, multiply n^m and then sum over n on both sides of master equations. In principle, moment equations are equivalent to original master equations if we can include all moment equations to the infinite order. Since an infinite number of moment equations are difficult to deal with, we introduce the Hartree-type approximation and the Poisson assumption to find a smaller, more manageable set of moment equations up to the first order moments. The Hartree-type approximation, an approximation for electron wave functions in multielectron atoms, considers the probability distribution for each type of protein separated from that of the other and only has a mean-field type of effect on the other, which means $P_{ijkl}(n_A, n_R) \approx P^A_{ij}(n_A) P^R_{kl}(n_R)$. In addition, the Poisson assumption of concentration distributions: $P^A_{ij}(n_A) = c^A_{ij} \frac{(\langle n_A \rangle_{ij})^{n_A}}{n_A!} e^{-\langle n_A \rangle_{ij}}$ and $P^R_{ij}(n_R) = c^R_{ij} \frac{(\langle n_R \rangle_{ij})^{n_R}}{n_R!} e^{-\langle n_R \rangle_{ij}}$, can truncate moment equations up to the first order. Therefore, we reached a close form of 16 deterministic moment equations, which only involve zero order moments $c^{A(R)}_{ij}$ and first order moments $\langle n_{A(R)} \rangle_{ij}$, as

$$\frac{dc^A_{11}}{dt} = -\frac{h_{AA}}{2} c^A_{11} \langle n_A \rangle^2_{11} + f_{AA} c^A_{01} - \frac{h_{AR}}{24} c^A_{11} \langle n_R \rangle^4 + f_{AR} c^A_{10} \tag{17}$$

$$\frac{dc^A_{10}}{dt} = -\frac{h_{AA}}{2} c^A_{10} \langle n_A \rangle^2_{11} + f_{AA} c^A_{00} + \frac{h_{AR}}{24} c^A_{11} \langle n_R \rangle^4 - f_{AR} c^A_{10} \tag{18}$$

$$\frac{dc^A_{11}}{dt} = \frac{h_{AA}}{2} c^A_{11} \langle n_A \rangle^2_{11} - f_{AA} c^A_{01} - \frac{h_{AR}}{24} c^A_{01} \langle n_R \rangle^4 + f_{AR} c^A_{00} \tag{19}$$

$$\frac{dc^A_{10}}{dt} = \frac{h_{AA}}{2} c^A_{10} \langle n_A \rangle^2_{11} - f_{AA} c^A_{00} + \frac{h_{AR}}{24} c^A_{01} \langle n_R \rangle^4 - f_{AR} c^A_{00} \tag{20}$$

$$\frac{dc^R_{11}}{dt} = -\frac{h_{RA}}{2} c^R_{11} \langle n_A \rangle^2 + f_{RA} c^A_{01} - \frac{h_{RR}}{24} c^R_{11} \langle n_R \rangle^4_{11} + f_{RR} c^R_{10} \tag{21}$$

$$\frac{dc^R_{10}}{dt} = -\frac{h_{RA}}{2} c^R_{10} \langle n_A \rangle^2 + f_{RA} c^A_{00} + \frac{h_{RR}}{24} c^R_{11} \langle n_R \rangle^4_{11} - f_{RR} c^R_{10} \tag{22}$$

$$\frac{dc^R_{11}}{dt} = \frac{h_{RA}}{2} c^R_{11} \langle n_A \rangle^2 - f_{RA} c^A_{01} - \frac{h_{RR}}{24} c^R_{01} \langle n_R \rangle^4_{11} + f_{RR} c^R_{00} \tag{23}$$

$$\frac{dc^R_{10}}{dt} = \frac{h_{RA}}{2} c^R_{10} \langle n_A \rangle^2 - f_{RA} c^A_{00} + \frac{h_{RR}}{24} c^R_{01} \langle n_R \rangle^4_{11} - f_{RR} c^R_{00} \tag{24}$$

$$\frac{d(c_{11}^A\langle n_A\rangle_{11})}{dt} = c_{11}^A(g_A^{11} - k_A\langle n_A\rangle_{11}) - \frac{h_{AA}}{2}c_{11}^A(\langle n_A\rangle_{11}^3 + 2\langle n_A\rangle_{11}^2) + f_{AA}c_{01}^A(\langle n_A\rangle_{01} + 2)$$
$$-\frac{h_{AR}}{24}c_{11}^A\langle n_A\rangle_{11}\langle n_R\rangle^4 + f_{AR}c_{10}^A\langle n_A\rangle_{10} \quad (25)$$
$$\frac{d(c_{10}^A\langle n_A\rangle_{10})}{dt} = c_{10}^A(g_A^{10} - k_A\langle n_A\rangle_{10}) - \frac{h_{AA}}{2}c_{10}^A(\langle n_A\rangle_{10}^3 + 2\langle n_A\rangle_{10}^2) + f_{AA}c_{00}^A(\langle n_A\rangle_{00} + 2)$$
$$+\frac{h_{AR}}{24}c_{11}^A\langle n_A\rangle_{11}\langle n_R\rangle^4 - f_{AR}c_{10}^A\langle n_A\rangle_{10} \quad (26)$$
$$\frac{d(c_{01}^A\langle n_A\rangle_{01})}{dt} = c_{01}^A(g_A^{01} - k_A\langle n_A\rangle_{01}) + \frac{h_{AA}}{2}c_{11}^A\langle n_A\rangle_{11}^3 - f_{AA}c_{01}^A\langle n_A\rangle_{01}$$
$$-\frac{h_{AR}}{24}c_{01}^A\langle n_A\rangle_{01}\langle n_R\rangle^4 + f_{AR}c_{00}^A\langle n_A\rangle_{00} \quad (27)$$
$$\frac{d(c_{00}^A\langle n_A\rangle_{00})}{dt} = c_{00}^A(g_A^{00} - k_A\langle n_A\rangle_{00}) + \frac{h_{AA}}{2}c_{10}^A\langle n_A\rangle_{10}^3 - f_{AA}c_{00}^A\langle n_A\rangle_{00}$$
$$+\frac{h_{AR}}{24}c_{01}^A\langle n_A\rangle_{01}\langle n_R\rangle^4 - f_{AR}c_{10}^A\langle n_A\rangle_{00} \quad (28)$$
$$\frac{d(c_{11}^R\langle n_R\rangle_{11})}{dt} = c_{11}^R(g_R^{11} - k_R\langle n_R\rangle_{11}) - \frac{h_{RA}}{2}c_{11}^R\langle n_A\rangle^2 + f_{RA}c_{01}^R\langle n_R\rangle_{01}$$
$$-\frac{h_{RR}}{24}c_{11}^R(\langle n_R\rangle_{11}^5 + \langle n_R\rangle_{11}^4) + f_{RR}c_{10}^R(\langle n_R\rangle_{10} + 4) \quad (29)$$
$$\frac{d(c_{10}^R\langle n_R\rangle_{10})}{dt} = c_{10}^R(g_R^{10} - k_R\langle n_R\rangle_{10}) - \frac{h_{RA}}{2}c_{10}^R\langle n_A\rangle^2 + f_{RA}c_{00}^R\langle n_R\rangle_{00}$$
$$+\frac{h_{RR}}{24}c_{11}^R\langle n_R\rangle_{11}^5 - f_{RR}c_{10}^R\langle n_R\rangle_{10} \quad (30)$$
$$\frac{d(c_{01}^R\langle n_R\rangle_{01})}{dt} = c_{01}^R(g_R^{01} - k_R\langle n_R\rangle_{01}) + \frac{h_{RA}}{2}c_{11}^R\langle n_A\rangle^2 - f_{RA}c_{01}^R\langle n_R\rangle_{01}$$
$$-\frac{h_{RR}}{24}c_{01}^R(\langle n_R\rangle_{01}^5 + \langle n_R\rangle_{01}^4) + f_{RR}c_{00}^R(\langle n_R\rangle_{00} + 4) \quad (31)$$
$$\frac{d(c_{00}^R\langle n_R\rangle_{00})}{dt} = c_{00}^R(g_R^{00} - k_R\langle n_R\rangle_{00}) + \frac{h_{RA}}{2}c_{10}^R\langle n_A\rangle^2 - f_{RA}c_{00}^R\langle n_R\rangle_{00}$$
$$+\frac{h_{RR}}{24}c_{01}^R\langle n_R\rangle_{01}^5 - f_{RR}c_{00}^R\langle n_R\rangle_{00} \quad (32)$$

where

$$\langle n_R\rangle^m = c_{11}^R\langle n_R\rangle_{11}^m + c_{10}^R\langle n_R\rangle_{10}^m + c_{01}^R\langle n_R\rangle_{01}^m + c_{00}^R\langle n_R\rangle_{00}^m$$
$$\langle n_A\rangle^m = c_{11}^A\langle n_A\rangle_{11}^m + c_{10}^A\langle n_A\rangle_{10}^m + c_{01}^A\langle n_A\rangle_{01}^m + c_{00}^A\langle n_A\rangle_{00}^m$$
$$(33)$$

Deterministic moment equations as in equ. (17)∼ (32) have the same form as the deterministic rate equations in the large volume limit for the master equations as equ. (1) ∼ (16). They can give oscillation solutions. The solutions are different to the ensemble average of stochastic simulation trajectories which can be written as: $\overline{n}(t) = \sum_n nP(n,t)$. In general, the solution $P(n,t)$ of master equation will reach a time independent steady state $P_{SS}(n)$ [2], which leads to time independent $\overline{n}$ after a long time. Therefore, the ensemble average of stochastic simulation trajectories will not give an oscillation solution.

The deterministic trajectories of the dual-feedback network for the activator A and the repressor R for different ω_{RA} are shown in Fig. 1(a), 1(b), 1(c), 1(d), 1(e), 1(f). In the n_A-n_R plane, they form closed limit cycles, as shown in Fig. 2(a), 2(b), 2(c), 2(d), 2(e), 2(f).

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The distribution landscapes of the dual-feedback network, in which two genes mutually repress and activate each other with self activation and self repression, are shown in Fig. 3. We noticed sharp Mexican hats in the nonadiabatic regime Fig. 3 (a) and the adiabatic regime Fig. 3 (f), which indicate robust oscillations (limit cycles).

The distribution landscapes of the network of the single loop negative feedback with one intermediate step are shown in Fig. 4. We noticed sharp Mexican hats in the nonadiabatic regime Fig. 4 (a) and Fig. 4 (b), which indicate robust oscillations (limit cycles).

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SUPPORTING REFERENCES

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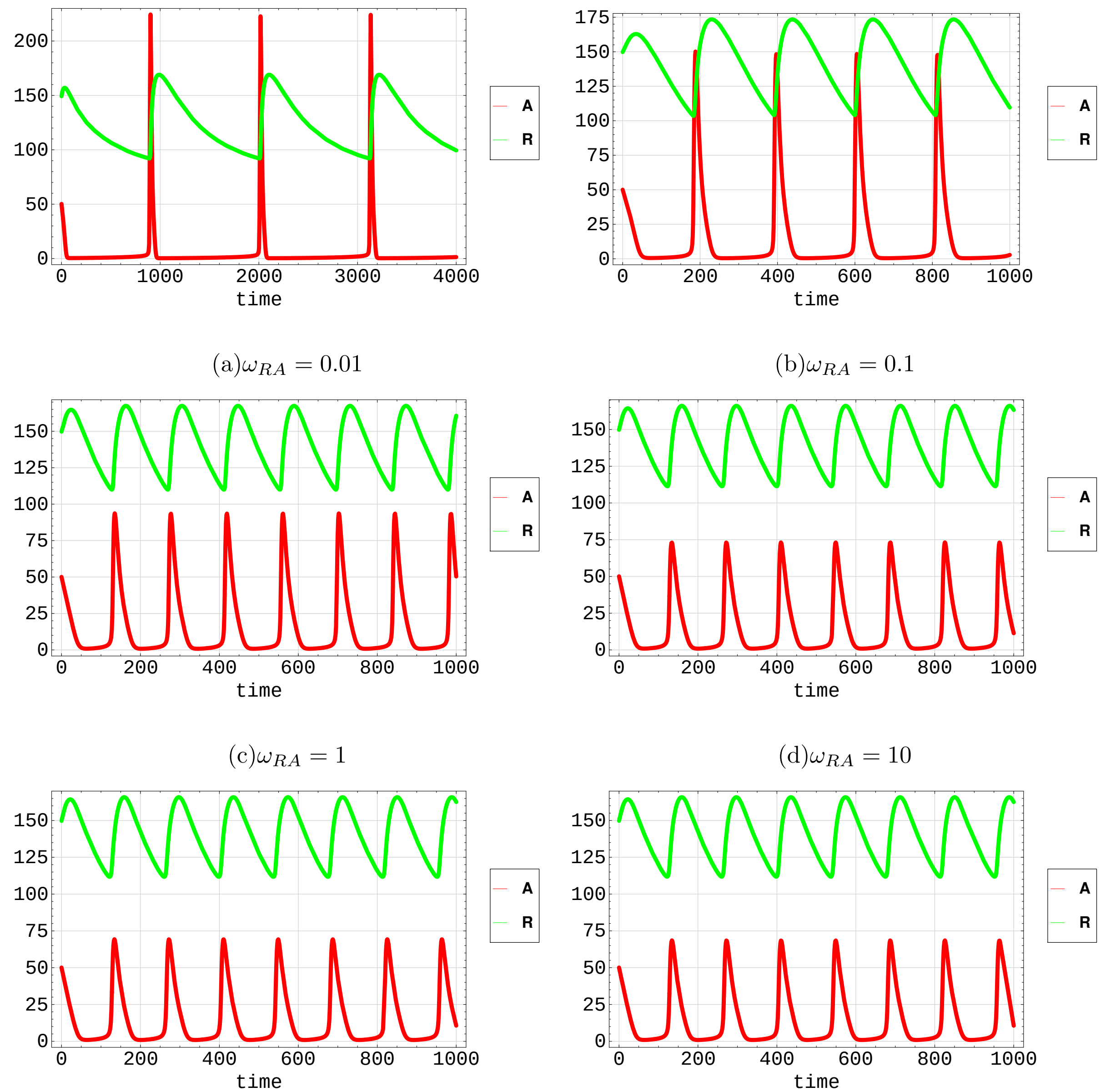
[2] Gardiner, C. 2004 Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences. Springer-Verlag: Berlin.



(a)$\omega_{RA} = 0.01$

(b)$\omega_{RA} = 0.1$

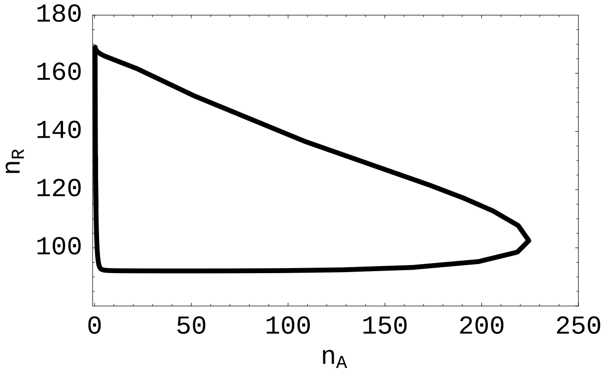
(c)$\omega_{RA} = 1$

(d)$\omega_{RA} = 10$

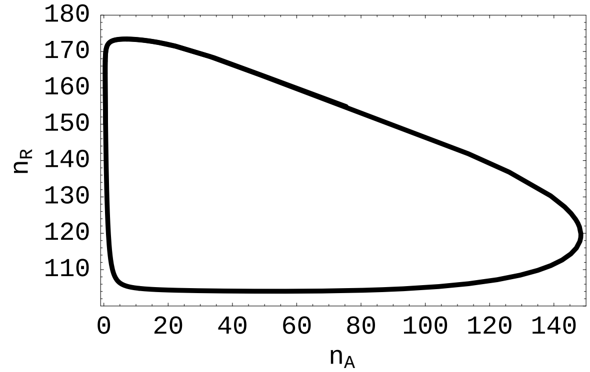
(e)$\omega_{RA} = 100$

(f)$\omega_{RA} = 1000$

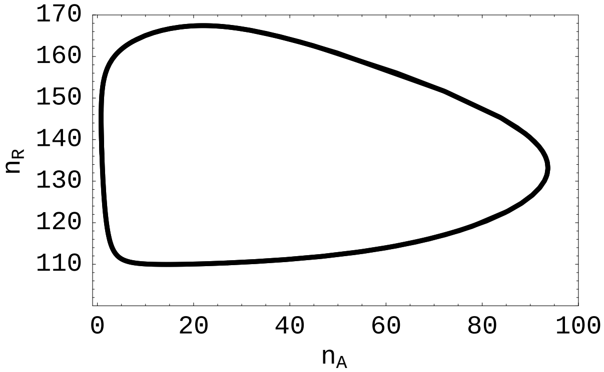
FIG. 1. The deterministic trajectories of the dual-feedback network for activator A (red) and repressor R (green) for different ω_{RA}.



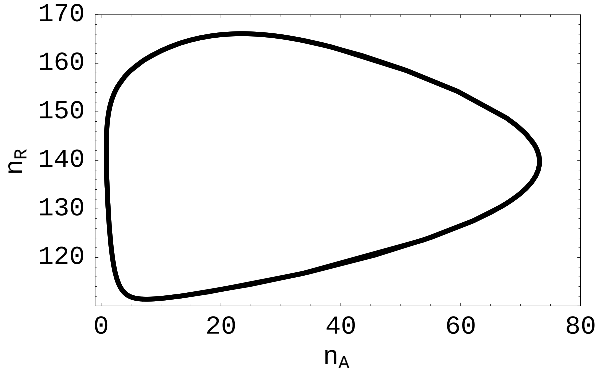
(a)$\omega_{RA} = 0.01$



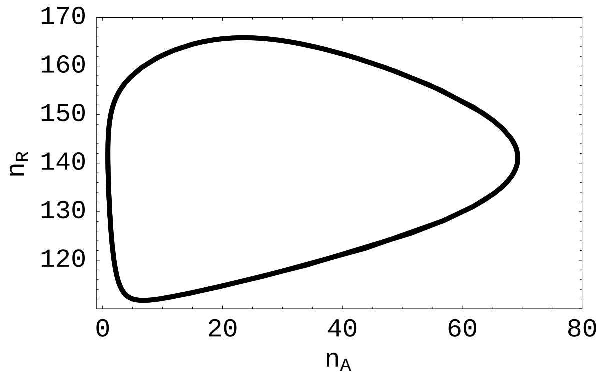
(b)$\omega_{RA} = 0.1$



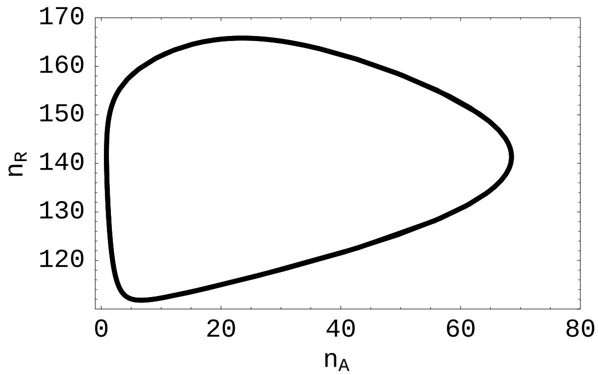
(c)$\omega_{RA} = 1$



(d)$\omega_{RA} = 10$

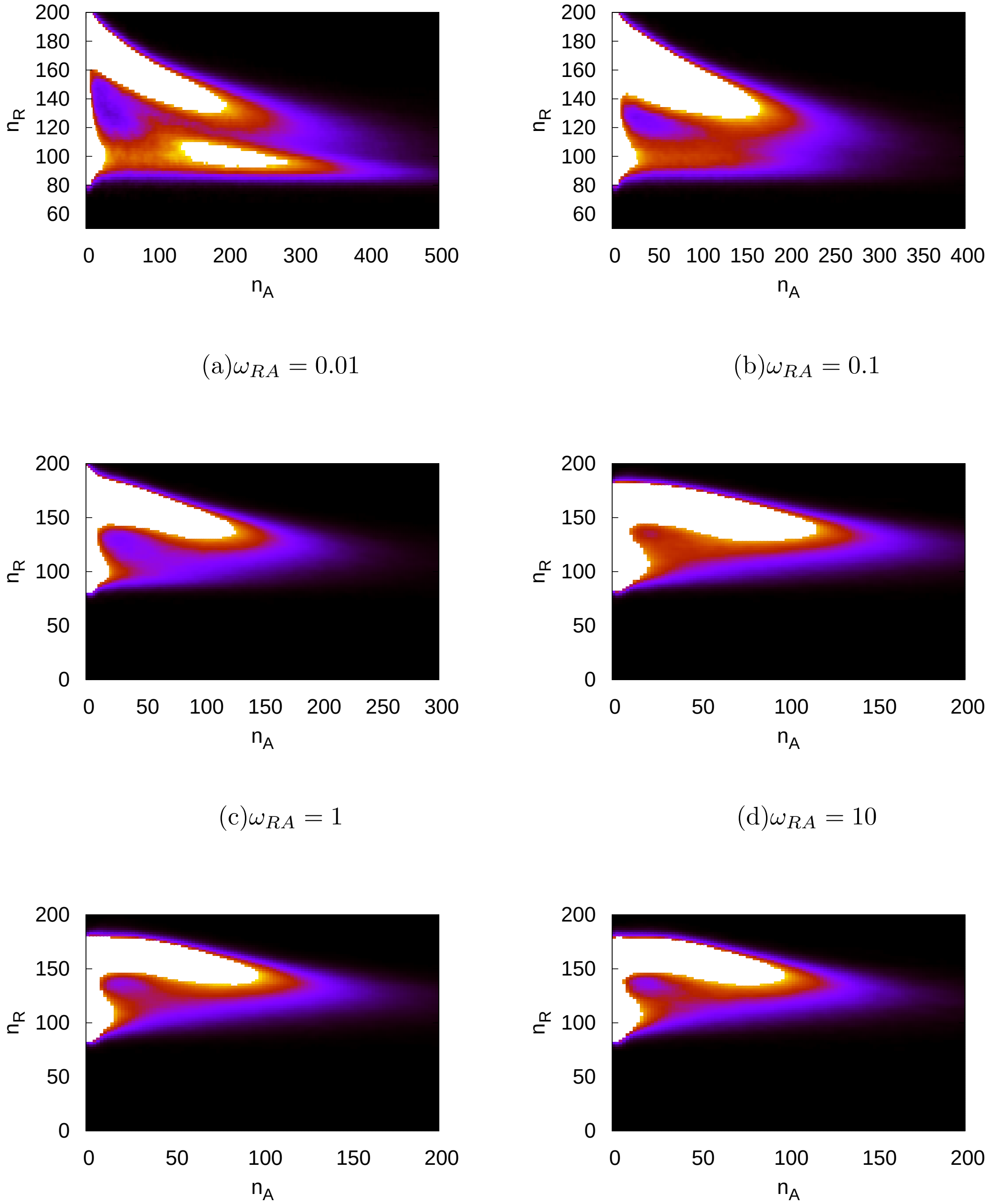


(e)$\omega_{RA} = 100$



(f)$\omega_{RA} = 1000$

FIG. 2. The deterministic trajectories of the dual-feedback network in n_A-n_R plane for different ω_{RA}.

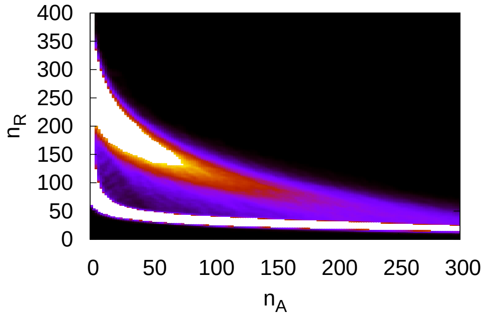


(a)$\omega_{RA} = 0.01$ (b)$\omega_{RA} = 0.1$

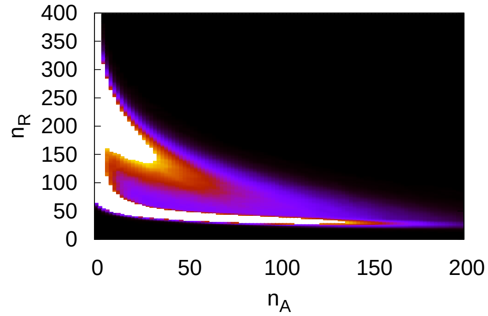
(c)$\omega_{RA} = 1$ (d)$\omega_{RA} = 10$

(e)$\omega_{RA} = 100$ (f)$\omega_{RA} = 1000$

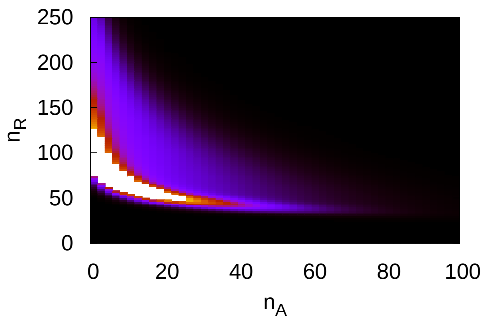
FIG. 3. Probability distribution landscapes of the dual-feedback network in n_A-n_R plane for different binding/unbinding rate ω_{RA}. Most robust oscillations in (a) the non-adiabatic and (d) the adiabatic regime companied with sharpest Mexican hats.



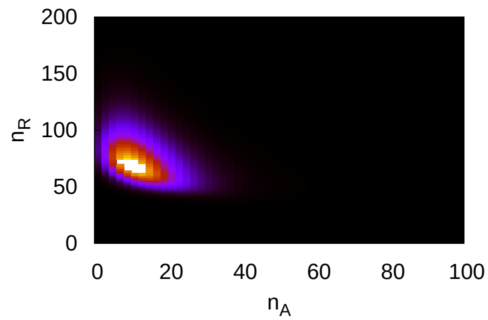
(a)$\omega_{RA} = 0.01$



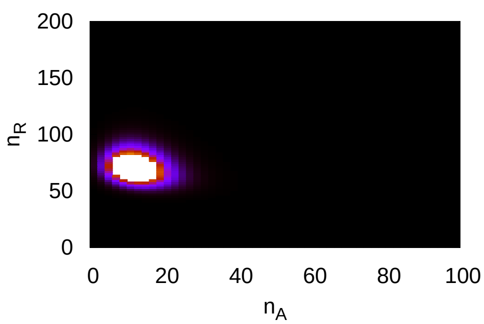
(b)$\omega_{RA} = 0.1$



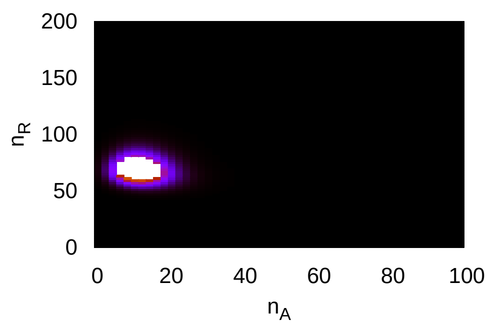
(c)$\omega_{RA} = 1$



(d)$\omega_{RA} = 10$



(e)$\omega_{RA} = 100$



(f)$\omega_{RA} = 1000$

FIG. 4. Probability distribution landscapes of the network of the single loop negative feedback with one intermediate step in n_A-n_R plane for different binding/unbinding rate ω_{RA}. Most robust oscillations in the non-adiabatic regimes (a) and (b), companied with sharpest Mexican hats.