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Tandem adaptation with a common design in *Escherichia coli* chemotaxis

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Abstract

We analyze a model for motor-level adaptation in *Escherichia coli* based upon the premise that clockwise (CW) and counter-clockwise (CCW) states have different preferred numbers of FliM subunits. We show that this model provides a simple mechanism for the recently observed motor-level adaptation, and it also explains the long-lasting puzzle on the thresholds observed when tethered cells are used to monitor responses to temporal ramps. We note that the motor-level adaptation has the same negative-feedback network design as the upstream receptor-level adaptation, and the tandem architecture of one control circuit followed by the other mitigates the effects of cell-to-cell variation and broadens the range of stimuli over which cells optimally respond.

I. INTRODUCTION

Cells need to adapt in order to function in an unsteady environment. This adaptation is carried out by biochemical networks that contain negative-feedback control mechanisms. One well-studied example is the receptor-level adaptation in *E. coli* chemotaxis [10]. Upon binding of chemoeffector ligands, the bacterial chemoreceptors change their conformations and the activity of a receptor kinase, which affects the phosphorylation rate of the downstream response regulator CheY. Phosphorylated CheY, CheY-P, controls the rotational bias of the bacterial flagellar motor by binding to FliM, a component in the C-ring. Over a time scale longer than that of receptor activation and CheY phosphorylation, the system adapts by methylation and demethylation of the chemoreceptors, catalyzed by CheR and CheB, respectively. The receptor kinase activity is enhanced by methylation, but the rate of methylation is suppressed by the receptor kinase activity. A negative feedback loop ($m \rightarrow \text{activity} \rightarrow m$) is thus formed to facilitate receptor-level adaptation, as shown in Fig. 1(a). The dynamics of this feedback control mechanism has been studied quantitatively by experiment [1, 3, 16] and by theoretical modeling [2, 17, 18].

Recently, experiments by Yuan et. al. [19] show that the bacterial flagellar motor can adapt partially to changes in the intracellular level of CheY-P by changing its composition. Here, we consider a simple model to account for this motor-level adaptation in which the feedback controller is the number of FliM monomers in the C-ring, and the feedback dynamics is based on FliM exchange [7, 19]. Specifically, we assume that the on and off rates of monomers of FliM to the C-ring depend solely upon the CCW and CW states of the motor (Pushkar Lele & Richard Branch, private communication). Our model shows good agreement with the observed motor-level adaptation. Furthermore, it explains why thresholds are observed when one measures responses to exponential ramps of chemoattractants using tethered cells [3] but not when using CheZ/CheY FRET [16]. We end our paper with a discussion of the significance for bacterial chemotaxis of having two adaptation mechanisms in tandem.

II. RESULTS

A. Partial adaptation of the *E. coli* flagellar motor switch

The C-ring of the *E. coli* flagellar motor contains a ring of FliM monomers. The dynamics of the size of the FliM ring can be described by:

$$dN/dt = k_{on}(B, N) - k_{off}(B, N), \quad (1)$$

where k_{on} and k_{off} are the on and off rates of FliM monomers, B is the CW bias, and N is the number of FliM monomers in the FliM ring. The CW bias depends upon the CheY-P concentration $[Y]$ and upon N . A simple Monod-Wyman-Changeux (MWC) [14] model can be used to describe the motor's highly cooperative switching behavior [6, 8]:

$$B = \frac{L(1 + [Y]/K_1)^N}{L(1 + [Y]/K_1)^N + (1 + [Y]/K_2)^N}, \quad (2)$$

with L the equilibrium constant for transitions between the CW and CCW states, and K_1 , $K_2 (> K_1)$ the dissociation constants for binding of CheY-P to FliM for the CW and CCW states, respectively.

This is a coarse-grained model on a time scale much longer than the average dwell time of the CW and CCW states, and therefore the CW and CCW states of the motor can be described by the CW bias B . For a constant CheY-P level $[Y]$, the steady state can be determined by

$$k_{on}(B, N) = k_{off}(B, N), \quad (3)$$

with a solution $N = N_a(B)$, where N_a represents the adapted value of N .

We first consider the general shape of the function $N_a(B)$, and its consequences for adaptation. When $[Y]$ increases, B increases, as clear from Eq. 2. Since B also increases with N , adaptation occurs when N decreases, which can be achieved if $N = N_a(B)$ is a decreasing function of B . This negative feedback mechanism for the motor-level adaptation is shown in Fig. 1(a). It is interesting to notice the parallel between the motor-level adaptation and the receptor-level adaptation mechanism, which is also shown in Fig. 1(a). For motor adaptation, the feedback controller is the number of FliM in the C-ring; for receptor adaptation, the feedback controller is the number of methyl groups in the receptors. The strength of the feedback mechanism, characterized by $N'_a(\equiv dN_a/dB)$, the slope of the function N_a , determines the accuracy of the motor-level adaptation. For $N'_a = 0$, N does not change and remains fixed (a FliM ring of fixed size), and there is no motor-level adaptation at all. At the other extreme, if $N'_a = -\infty$, the solution to Eq. (1) is $B \approx B_0$, independent of N , and the system adapts "perfectly" to $B = B_0$.

In general, the steeper the slope $N'_a(B_0)$, the more accurate the adaptation. If $N_a(B)$ has a sigmoidal shape, decreasing sharply near $B = B_0$, then the adapted motor CW bias B will have a plateau near B_0 for a range of $[Y]$. This last observation can explain the discrepancy between the switch-level responses to exponential ramps measured by Block et al. [3] and the CheY-P-level responses to the same ramps measured by Shimizu et al. [16] which will be explained in detail in a later section of the paper.

Detailed models for the on-off kinetics of the FliM monomers onto the C-ring can be developed by assuming that the preferred number of FliM molecules in the ring is different

in the CCW and CW states. This difference could be caused by the different conformations of the FliM protein in the CCW and CW states. In particular, we assume that the preferred ring size N_2 for the CCW ring is larger than the preferred ring size N_1 in the CW state, as shown in Fig. 1(b). The number of FliM units in the ring can thus vary between N_1 and N_2 depending on the CW bias of the motor. Here, we assume that a FliM monomer is incorporated into the C-ring with a probability rate k_1 when the motor is in the CCW state, and a FliM monomer is detached from the C-ring with a probability rate k_2 when the motor is in the CW state. Therefore we have:

$$k_{on}(B, N) = (1-B) \times k_1(N), \quad k_{off}(B, N) = B \times k_2(N). \quad (4)$$

Given the finite range of N : $N_1 \leq N \leq N_2$, k_{on} and k_{off} should vanish at the maximum ring size N_2 and the minimum ring size N_1 , respectively. A simple form of $k_1(N)$ and $k_2(N)$, which satisfies this requirement, is used here:

$$k_1(N) = \frac{k_{1,0}(N_2 - N)}{(N_2 - N) + \Delta N_1}, \quad k_2(N) = \frac{k_{2,0}(N - N_1)}{(N - N_1) + \Delta N_2}, \quad (5)$$

where $k_{1,0}$ and $k_{2,0}$ are rate constants for the on and off processes, respectively. For simplicity, we set $k_{1,0} = k_{2,0} = k_0$ for the simulations in this paper; k_0 determines the motor adaptation speed. ΔN_1 and ΔN_2 represent the sizes of the boundary region over which k_{off} and k_{on} decrease to zero. For simplicity, we set $\Delta N_1 = \Delta N_2 = \varepsilon(N_2 - N_1)$, where $\varepsilon < 1$ is the fraction of the boundary region.

The dynamics of N , given by Eq. 1, can thus be expressed explicitly as:

$$\frac{dN}{dt} = k_0 \left[\frac{(1-B)(N_2 - N)}{(N_2 - N) + \varepsilon(N_2 - N_1)} - \frac{B(N - N_1)}{(N - N_1) + \varepsilon(N_2 - N_1)} \right]. \quad (6)$$

Letting $dN/dt = 0$ in the equation above leads to the steady state (adapted) value of $N = N_a(B)$, with the function $N_a(B)$ given as:

$$N_a(B) = N_1 + \Delta N \frac{(1-2B-\varepsilon) + \sqrt{(1+2\varepsilon)(1-2B)^2 + \varepsilon^2}}{2(1-2B)}, \quad \text{when } B \leq 1/2 \\ = N_1 + \Delta N \frac{(1-2B-\varepsilon) - \sqrt{(1+2\varepsilon)(1-2B)^2 + \varepsilon^2}}{2(1-2B)}, \quad \text{when } B > 1/2, \quad (7)$$

where $\Delta N \equiv N_2 - N_1$. $N_a(B)$ decreases from N_2 to N_1 as B increases from 0 to 1 in a highly nonlinear fashion. As described before, the accuracy of motor adaptation is determined by the slope of $N_a(B)$ at its set point $B = B_0 = 1/2$. From Eq. 7, we have

$N'_a(B_0) = -(1+2\varepsilon)^{-1} \Delta N$, which diverges as $\varepsilon \rightarrow 0$. Therefore, smaller ε leads to more accurate adaptation. The steep slope $N'_a(B_0)$ for small ε in our model has the same origin as the zeroth-order ultrasensitivity in reversible enzyme reactions [9]. For $\varepsilon \ll 1$, there is a large region of N between N_1 and N_2 where k_{on} and k_{off} only depend strongly on B : $k_{on} \approx k_0(1 - B)$, $k_{off} \approx k_0 B$. Therefore, a small change in B near B_0 , where $k_{on} = k_{off}$, drives the system to one of its two boundaries: $N = N_1$ when $B > B_0$; $N = N_2$ when $B < B_0$.

We now demonstrate the motor-level adaptation quantitatively with our model. For a given value of the CheY-P level $[Y]$, the adapted state can be determined by the dependence of B on N , given by Eq. 2, and the dependence of the adapted $N(N_a)$ on B , given by Eq. 7. This is shown in Fig. 2(a) where the adapted states, labeled by the circles, are the intercepts of Eq. 2 (red lines), shown for different values of $[Y]$, and Eq. 7 (black line). The adapted

values of B for different values of $[Y]$ are shown in Fig. 2(b) (solid blue line). For comparison, we have also plotted the dependence of B on $[Y]$ for the non-adaptive model, i.e., Eq. 2 with fixed values of N . Clearly, the adapted motor bias remains roughly constant near B_0 for a wide range of $[Y]$, whereas B quickly deviates from B_0 in the non-adaptive model with fixed values of N . The accuracy of the motor-level adaptation and the adaptation range can be understood from Fig. 2(a). For strong negative feedback characterized by a steep $N_a(B)$ function (the steep part of the black line in Fig. 2(a)), the adapted states have a roughly constant B . The region of accurate adaptation is limited by the finite range of adjustable N , as shown by the termination of the steep region of the black line in Fig. 2(a) near $N = N_1 = 30$ and $N = N_2 = 38$. Finally, the response dynamics of the motor bias and of the average number of FliM molecules in the C-ring to a series of step changes in CheY-P level are shown in Fig. 3.

B. The effect of motor-level adaptation: origin of the thresholds in ramp responses

In wild-type cells, the effects of motor-level adaptation are mixed with those of the receptor-level adaptation and are therefore hard to observe. However, time-varying stimuli, especially exponential ramps, can lead to a constant shift of the intracellular CheY-P level, as shown directly in the recent FRET experiments by Shimizu et al. [16]. This shift in CheY-P level can be understood in a simple model of the receptor-level adaptation, wherein the dynamics of the receptor methylation level m is controlled by the activity of the receptor a :

$$dm/dt = F(a), \quad (8)$$

where the methylation rate function $F(a)$ only depends on a ; the perfectly adapted activity a_0 is the root of the monotonically decreasing $F(a)$ at $F(a_0) = 0$. The activity a depends upon the chemoeffector concentration $[L]$ and m . Here, a MWC type model is used:

$$a = \left(1 + \exp\left(N_r \left(\ln \frac{1 + [L]/K_i}{1 + [L]/K_a} - \alpha(m - m_0)\right)\right)\right)^{-1}, \quad (9)$$

where N_r is the size of the tightly coupled MWC cluster, $K_i, K_a (\gg K_i)$ are the dissociation constants of the chemoeffector ligand to the inactive and the active receptors respectively, and α and m_0 are constants characterizing the methylation-level-dependent free energy contribution [17].

For an exponential ramp stimulus $[L] \sim \exp(rt)$ within the range $K_i \ll [L] \ll K_a$, the activity is driven away from a_0 and reaches a new steady-state value a_r , which satisfies:

$$F(a_r) = \frac{r}{\alpha}. \quad (10)$$

The values of a_r have been directly measured for different values of r (for both up and down ramps) by Shimizu et al. [16], from which the methylation rate function $F(a)$ was determined quantitatively. It was found that $F(a)$ has a linear dependence on a , $F(a) \approx F'(a_0)(a - a_0)$, in a large region around $a = a_0$. Equivalently, the ramp response characterized by the shift in activity $\Delta a \equiv a - a_0$ is linearly proportional to the ramp rate r : $\Delta a \approx (\alpha F'(a_0))^{-1} r$ for a large range of r around $r = 0$. No threshold in r was observed. However, Block et al. [3] reported threshold behavior when using tethered cells to measure changes in rotational bias in response to exponential ramps. The measured response was very small when the ramp rate was below a certain threshold value. This seems to be in contradiction with the absence of a threshold in the FRET experiments [16].

Here, we show that this “discrepancy” can be resolved by the motor-level adaptation. For a small ramp rate, the shift in receptor kinase activity and the CheY-P level is small. Due to the ultrasensitivity of the motor switch, this change in CheY-P level leads to a large change in motor bias, as shown in Fig. 4(a). However, if the CheY-P level is within the range of motor adaptation, the motor bias will recover (adapt) back to its pre-stimulus level, which leads to an almost unchanged steady-state motor bias, as shown in Fig. 4(a) for the case of $r = 0.04$. For a large ramp rate, the shifted CheY-P level lies outside of the adaptation range of the motor, which leads to a large change in the steady-state motor bias, as shown in Fig. 4(a) for the case of $r = 0.12$. The thresholds in the ramp rate for the motor response are therefore caused by the motor-level adaptation, and the threshold values are determined by the range of this adaptation. In Fig. 4(b), we have plotted the steady-state value of the CCW bias for different ramp rates (both positive and negative) from our model. The thresholds are clear from the plot, in agreement with the observations of Block et al. [3]. It should be noted that a smooth linear dependence of the CheY-P level on the ramp rate comes naturally from our model, in agreement with the observations of Shimizu et al. [16]. Therefore, our model with the receptor-level and motor-level adaptation in tandem resolves the disagreement between ramp responses measured at the kinase level and the motor-level.

The values of the ramp thresholds can be determined analytically from our model. We denote $K_{\frac{1}{2}}(N)$ as the CheY-P level at CW bias B_0 for a FliM ring of fixed size N (we set $B_0 = 1/2$ in this paper). From Eq. 2, we have:

$$K_{\frac{1}{2}}(N) = \frac{1-L^{1/N}}{L^{1/N}-C} K_1, \quad (11)$$

where $C \equiv K_1/K_2$. For $\varepsilon \ll 1$, the range of $[Y]$ over which the motor can adapt is given by $[Y]_1 (\equiv K_{\frac{1}{2}}(N_1))$ and $[Y]_2 (\equiv K_{\frac{1}{2}}(N_2))$, see Fig. 2(b). For $r = 0$, i.e., a constant stimulus, the activity is adapted to $a = a_0$, the C-ring size is at its baseline value $N = N_0$, and the CheY-P level is at its set value $[Y]_0 (\equiv K_{\frac{1}{2}}(N_0))$. An exponential ramp with ramp rate r causes a shift in activity $\Delta a(r) = r/(\alpha F'(a_0))$, which leads to a change $\Delta[Y]$ in the CheY-P level. The up and down ramp thresholds, $r_{t,+}$ and $r_{t,-}$, correspond to the values of r that drive $[Y]$ to reach $[Y]_2$ and $[Y]_1$, respectively. Near $a = a_0$, we assume $[Y]$ is linearly proportional to a , which leads to: $\Delta a(r_{t,+(-)})/a_0 = ([Y]_{2(1)} - [Y]_0)/[Y]_0$. By using the expression for Δa and Eq. 11 for $[Y]_0$, $[Y]_1$, and $[Y]_2$, we obtain the expressions for $r_{t,+}$ and $r_{t,-}$:

$$\begin{aligned} r_{t,+} &= \alpha a_0 F'(a_0) \times \frac{(L^{1/N_0} - L^{1/N_2})(1-C)}{(1-L^{1/N_0})(L^{1/N_2}-C)}, \\ r_{t,-} &= \alpha a_0 F'(a_0) \times \frac{(L^{1/N_0} - L^{1/N_1})(1-C)}{(1-L^{1/N_0})(L^{1/N_1}-C)}. \end{aligned} \quad (12)$$

Besides their dependence on the motor parameters, both thresholds depend linearly on $\alpha a_0 F'(a_0)$, which was measured to be $\sim -0.03 s^{-1}$ (at $32^\circ C$) by the FRET experiments [16]. By using this value of $\alpha a_0 F'(a_0)$ in Eq. 12, together with the values of the motor parameters used in our study ($N_1 = 30$, $N_2 = 38$, $N_0 = 34$, $K_1/K_2 = 0.25$, $L = 2^{-34}$), we estimate $r_{t,+} \sim 0.006 s^{-1}$ and $r_{t,-} \sim -0.01 s^{-1}$, which agree with the thresholds observed in reference [3].

III. DISCUSSION

It is now well established that the mechanism for the heightened sensitivity is fundamentally the same for the MCP cluster [4, 13] and the motor switch [6, 8]: they are both caused by the cooperative interaction of the subunits in the functional complexes. Here, we note that the proposed mechanism for the motor-level adaptation also shows a strong resemblance to the adaptation mechanism at the receptor level, as illustrated in Fig. 1(a). The output of the

motor switch circuit, namely the bias of the motor, feeds back to control a key component of the switch, i.e., the number of FliM subunits in the switch, which brings the motor bias back towards a certain preferred level. This is exactly what happens in the receptor-level adaptation. The similarity between the two adaptation modules is evident in Fig. 1(a) with the following correspondences:

$$[\text{CheY-P}] \leftrightarrow [L]; B \leftrightarrow \text{activity}; m \leftrightarrow N.$$

For the dynamics, just like in the case of receptor-level adaptation, motor-level adaptation occurs at a much longer time scale ($> 10\text{s}$) than the actual motor switching time ($\sim 1\text{s}$). Thus, effectively, it is the average property of the switching dynamics, characterized by the motor bias, which controls the number of FliM in the ring. However, there is at least one detailed difference. While an MCP cluster adapts by changing a property (methylation level) of its individual subunits, the motor switch adapts by changing the number of its subunits. There are reports of MCP cluster size variation in response to signaling [11], however, they remain in dispute [5].

The key assumption made here for the mechanism of motor-level adaptation is that the CW motor and the CCW motor have (at least on average) different numbers of FliM subunits. If the FliM structure is different in the CCW and CW motors, like what has been established for FliG [12, 15], then this assumption is highly plausible. However, we do not know the exact values of N_1 and N_2 ; and whether all FliM's in a given motor are incorporated into the C-ring or whether some of them only are attached peripherally remains to be determined. These information will further refine our model.

As shown previously in the case of receptor-level adaptation, the accuracy of adaptation is determined by how the kinetics of the controller (the receptor methylation level m) depends on itself and the output (the receptor activity a) that it controls. Accurate adaptation can be achieved when the controller dynamics depends strongly on the output but only weakly (or not at all) on the value of the controller itself. For example, accurate receptor-level adaptation is guaranteed by the methylation rate function $F(a)$ only dependent on a but not m . In the case of motor-level adaptation, the adaptation kinetics is controlled by the on and off rates (k_{on} and k_{off}) of the FliM subunits to the C-ring. Generally, k_{on} and k_{off} depend on the number N of FliM in the C-ring, especially near the extreme (boundary) values of N : N_1 and N_2 , where one of them vanishes: $k_{on}(N_2) = 0$, $k_{off}(N_1) = 0$. In our model (Eqs. 4 and 5), the size of the boundary regions is given by $\varepsilon \times (N_2 - N_1)$. For $\varepsilon \ll 1$, away from the two boundary regions, there is a region of N where both k_{on} and k_{off} have weak dependence on N , and only depend on B : $k_{on} \approx k_{1,0}(1 - B)$, $k_{off} \approx k_{2,0}B$. This region, the steep part of the black line in Fig. 2(a), defines the partial adaptation regime for the motor. This hypothesized sigmoidal dependence of the adapted N versus the adapted B should be tested by future experiments. The adapted value of the motor bias $B_0 = k_{1,0}/(k_{1,0} + k_{2,0})$ is determined by the on and off rate constants $k_{1,0}$ and $k_{2,0}$, which can depend on the FliM concentration in the cell. Therefore, there could be a systematic dependence of the adapted motor bias on the FliM expression level, analogous to the dependence of the adapted MCP receptor activity on the expression level of CheR or CheB. This prediction should also be checked by future experiments.

Adaptation is a fundamental life process that all biological systems rely on to survive in a changing environment. It is quite remarkable that *E. coli* has developed a multi-level adaptation system, where the mechanism at each level follows the same design principle. For the flagellar motor, the function of accurate adaptation is to make sure that the motor remains at the most sensitive part of its response curve. Even though the receptor-level

adaptation is highly accurate, the adapted level of CheY-P depends on the concentrations of other components in the pathway (such as CheR and CheB) and can vary from cell to cell. Therefore, motor-level adaptation is needed to allow normal motor function in the presence of the inevitable cell-cell variation. Moreover, there is an additional advantage for having motor-level adaptation in bacterial chemotaxis. Consider a free swimming *E. coli* cell chemotaxing in an exponential spatial gradient of attractant. As the cell moves up the spatial gradient, the average attractant concentration that the cell senses increases exponentially in time. As we have shown before, an exponential temporal ramp leads to a constant decrease in receptor activity even with the perfect receptor-level adaptation. The shift in the receptor activity caused by the ramp increases with the ramp rate or the steepness of the spatial gradient, and the resulting decrease in CheY-P level can take the motor outside of its sensitive regime. However, the motor-level adaptation mechanism, being downstream of CheY-P, allows the motor to adapt to the lowered CheY-P level and continue to operate in its most sensitive regime. Therefore, the motor-level adaptation broadens the range of spatial gradients to which cells can respond in an optimum way.

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Figure 1. Illustration of the models. (a) The *E. coli* chemotaxis pathway with two levels of adaptation. (b) A possible mechanism for the motor-level adaptation.

Figure 2.

The motor-level adaptation mechanism. (a) The black line represents the dependence of the adapted ring size on the CW bias B , i.e., $N = N_d(B)$, as given by Eq. 7. The red lines represent the dependence of B on the FlIM ring size N for different values of CheY-P levels, $[Y]$ (normalized by its maximum value), as given by Eq. 2. The adapted states for different CheY-P levels are labeled by circles. Parameters used are $\epsilon = 0.05$, $K_1 = 1$, $K_2 = 4$, $L = 2^{-34}$. (b) The CW bias of the adapted state versus the normalized CheY-P level $[Y]$ is shown by the blue line. For each value of $[Y]$, the motor adapts by reaching a different value of N between $N_1 = 30$ and $N_2 = 38$. The dotted lines show the dependence of B on $[Y]$ if N is fixed at $N = 30, 34, 38$.

Figure 3.

The adaptation kinetics of the number of FlhM molecules in the ring N and the CW bias B to sudden changes of CheY-P level $[Y]$. The black lines are for $[Y]: 0.5 \rightarrow 0.4 \rightarrow 0.5$; the red lines are for $[Y]: 0.5 \rightarrow 0.7 \rightarrow 0.5$.

Figure 4.

The ramp responses. (a) The dynamics of the normalized CheY-P level ($[Y]$) and the motor CW bias (B) in response to exponential ramps $[L] \sim \exp(rt)$ with different ramp rates $r = 0.04, 0.08, 0.12, 0.16$ (arbitrary units). The shift in steady-state activity (solid lines) depends linearly on r . For smaller ramp rates, the motor-level adaptation drives B (broken lines) back to its adapted level after an initial large change. For larger ramp rates, the recovery diminishes. The parameters used in the simulations are for the signaling model, $N_r = 6$, $K_f = 1$, $K_a = 1000$, $\alpha = 1.7$, $a_0 = 0.5$, and $F'(a_0) = -0.5$; for the motor adaptation model $\epsilon = 0.05$, $N_1 = 30$, $N_2 = 38$, and $k_0 = 1$. (b) The adapted (steady-state) values of B are shown for different exponential ramp rates r . The black and the red lines are for the up ($r > 0$) and down ($r < 0$) ramps, respectively. Thresholds appear near $r = 0$, where B remains nearly constant. This region corresponds to the flat part of the blue line in Fig. 2(b). The different thresholds for the up and the down ramps reflect the difference in the shapes of the response curves for $N = N_1 = 30$ and $N = N_2 = 38$, and the difference in their half-maximum CheY-P level $K_{\frac{1}{2}}$, as evident in Fig. 2(b).