From conformational spread to allosteric and cooperative models of E. coli flagellar motor

A Pezzotta\textsuperscript{1}, M Adorisio\textsuperscript{1} and A Celani\textsuperscript{2}

\textsuperscript{1} International School for Advanced Studies (SISSA), via Bonomea 265, I-34136 Trieste, Italy
\textsuperscript{2} The Abdus Salam International Centre for Theoretical Physics (ICTP), Strada Costiera 11, I-34014 Trieste, Italy
E-mail: apezzotta@sissa.it

Received 15 June 2016, revised 26 September 2016
Accepted for publication 21 December 2016
Published 6 February 2017

Abstract. Escherichia coli swims using flagella activated by rotary motors. The direction of rotation of the motors is indirectly regulated by the binding of a single messenger protein. The conformational spread model has been shown to accurately describe the equilibrium properties as well as the dynamics of the flagellar motor. In this paper we study this model from an analytic point of view. By exploiting the separation of timescales observed in experiments, we show how to reduce the conformational spread model to a coarse-grained, cooperative binding model. We show that this simplified model reproduces very well the dynamics of the motor switch.

Keywords: molecular motors, signal transduction, stochastic processes
1. Introduction

The ability to respond efficiently to chemical stimuli is essential for the survival of many animal species, ranging from prokaryotic cells to much more complex organisms such as insects or birds. At the microscale, the mechanism which allows organisms to move under the influence of chemical stimuli is called chemotaxis [1].

Escherichia coli (E. coli) is one of the model organisms for studies about bacterial chemotaxis [2]. Thanks to its flagella, activated by bi-directional rotary motors, E. coli is able to move towards more favorable environments by optimally alternating runs and tumbles, which consist, approximately, of straight lines and random ‘turns’ respectively.

The biochemical mechanisms underlying the chemotactic response of E. coli are well understood at the molecular level [3]. A sensing apparatus is devoted to detecting information about the environment, by measuring the concentration of chemicals (generally called, in this context, chemoeffectors). The arrangement and functioning of the receptors present in E. coli cellular membrane has been extensively investigated also from the theoretical point of view (see e.g. [4, 5]). The information collected by the receptors is transduced to the flagellar motors through the ‘messenger molecule’ CheY. The cytoplasmic concentration of its phosphorylated form CheY-P varies according to the activity of the membrane receptors. The CheY-P molecule then acts as a regulator of the activity of the flagella by binding to their motors. These are constituted by rings of Fli molecules, arranged in units called protomers. Motors are biased by the Fli
occupancies to rotate counterclockwise (CCW) or clockwise (CW). When all the motors are in the CCW state, the flagella form a bundle which propels the cell in a forward run; if at least one motor is in the CW state instead, the bundle splits apart and the cell tumbles.

This mechanism is an example of allosteric (or indirect) regulation, where the activity of protein complexes changes collectively upon independent binding of external molecules. The original model, which encodes the concept of co-operativity in indirect regulation, is the one proposed by Monod, Wyman and Changeux (MWC), commonly known as the concerted model [6, 7].

Shortly after the publication by MWC, Eigen realized that the concerted model can be extended in order to offer a more graded interplay between the interactions within allosteric complexes and their binding affinities [8]. When the interactions are local, this generalized model takes the name of conformational spread (see section 2) and is nowadays understood in a statistical mechanical framework, in the light of the ferromagnetic Ising model—to which it is formally equivalent [4, 9].

These allosteric models have found application in bacterial chemotaxis. In [10], the authors showed how the MWC model is able to reproduce the activity of the flagellar motor of *E. coli* as a function of the concentration of cytoplasmic CheY-P [10]. In this paper, the authors recognized that the balance between the different CheY-P affinity in the two activity states and the size of the motor protein complex was essential in explaining the observed cooperative behaviour of the switch. The MWC model turned out to be particularly suitable for describing the flagellar switch of *E. coli*, in that it accounts for the correct degree of co-operativity, given a proper choice of parameters values.

The conformational spread model has been applied to bacterial chemotaxis, both for the membrane receptors [4, 9] and for the flagellar rotary motors [11]. By means of a simulation of its associated Glauber dynamics [12], a numerical test of the conformational spread model against the experimental measurement of the rotation speed of the flagella has been performed [13]. Such analysis showed an excellent agreement between experiments and numerical simulations regarding several aspects of the dynamics, such as the switching time distribution at fixed values of the cytoplasmic CheY-P concentration and the sensitivity of the switch to small variations of CheY-P. A more detailed numerical analysis of the model followed up [14], in which other dynamical properties of the conformational spread model were also quantified (like the locked-state behaviour—viz. the time spent by the motor in a rotational state between two consecutive switches) and a more precise estimation of the values of the model parameters which best fit the experimental results was given.

From the analytical point of view, one major obstacle to the study of the conformational spread model resides in the large number of states. The one-dimensional nature of the ring allows nonetheless for an exact calculation of its partition function at equilibrium via the transfer matrix method [15]. However, no analytical treatment of the non-equilibrium behaviour of the model has ever been attempted, to our knowledge.

In this work we present an analytical derivation of the non-equilibrium properties of the conformational spread as a model of the flagellar switch. Our analysis hinges upon the presence of a hierarchy of widely separated time scales, as confirmed by experiment. Due to the strong interaction between the protomers, the coarsening of activity
domains in the ring is much faster than the nucleation of a domain (i.e. the transitions away from the state of all active or all inactive protomers). This allows the treatment of the whole motor as an allosteric switch in two different activity states (CW and CCW), essentially described by the MWC model. The nucleation of a domain is in turn much more frequent than the binding/unbinding of a CheY-P molecule by one protomer, which makes it possible to operate a quasi-static approximation for the number of bound CheY-P and get a description of the slow binding dynamics, to which the activity is slaved. This separation of timescales allows us to reduce the complexity of the full conformational spread dynamics by progressively averaging the faster degrees of freedom and obtain, in the end, an effective cooperative model which captures the relevant features of the flagellar switch on the slowest timescales. The effective rates of the emergent ‘coarse-grained’ cooperative binding model are expressed in terms of the rates of the original ‘microscopic’ conformational spread model. In short, the rationale of our approach can be schematically summarized as follows:

The paper is structured as follows: in section 2 we present the conformational spread model, outlining its equilibrium properties and introducing the dynamics (satisfying detailed balance) which is relevant for our study and is the object of our multiscale analysis; in section 3 we show that, given our experimentally justified assumptions, it is possible to reduce the conformational spread to the concerted MWC model; a further time-scale separation is the subject matter of section 4, resulting in a cooperative binding model (formally, a birth-and-death process with site-dependent rates) that is compared with experiment in section 5.

2. Conformational spread model

The ring of proteins forming the motor of the E. coli flagellum has been shown to be very well described by the conformational spread model [9, 11, 13]. This model consists of N identical units, or protomers, each of which can appear in two different states, active (A) or inactive (I): a protomer in the active state increases the probability of CW rotation of the motor; in the inactive state, of CCW rotation (see figure 1). Moreover, each protomer can also bind a ligand, corresponding to the CheY-P chemotactic regulator: we refer to the protomer as in the bound (B) state when a ligand is attached to it, or unbound (U) otherwise. Therefore, the single protomers can be in four different states, corresponding to all the possible activity and binding configurations.

The state diagram of a single protomer is depicted in figure 2: the A state is energetically more favorable than the I state when a ligand is bound and vice versa. This property ensures that this is a good model for allosteric regulation. Specifically, a bias in the activity of the motor depends on the number of bound CheY-P molecules: at fixed high concentration of cytoplasmic CheY-P (denoted by c) the motor will most probably spin clockwise. The state of the full system is specified by the sequence s = {⟨α1, ℓ1⟩, ..., ⟨αN, ℓN⟩}, where the subscripts label the N protomers, α indicates the

doi:10.1088/1742-5468/aa569e
From conformational spread to allosteric and cooperative models of *E. coli* flagellar motor

**Figure 1.** The flagellar motor. The Fli molecules are depicted in white (inactive state, *I*) and red (active state, *A*), while the grey spots represent the CheY-P regulator. The motor rotates counterclockwise when most of the protomers are in the inactive state (left) and clockwise otherwise (right).

**Figure 2.** State diagram and couplings in the conformational spread model. On the left, the energy levels of the single protomer states: the active (CW) configuration is energetically favorable in the unbound case (*ℓ* = 0), while the inactive (CCW) has lower energy when in the bound case (*ℓ* = 1); the binding regulates the activity of the protomers. The notation and the general scheme has been borrowed from [7]. On the right, the coupling energy: the ‘ferromagnetic’ coupling (independent of *ℓ*) accounts for the high sensitivity of the response of the ring upon binding.

activity state *A* or *I*, and *ℓ* stands for the binding state *B* (*ℓ* = 1) or *U* (*ℓ* = 0): hence, the number of possible configurations of the ring with *N* protomers is \((2 \times 2)^N\).

In addition, the protomers are coupled via a nearest neighbour interaction, which depends on their activity states only: in particular, the energy is lowered by a quantity *J* when the neighbouring protomers are in the same activity state *A* or *I*. It turns out that the activity of the ring (fraction of active protomers) is more sensitive to small variations of concentration of ligands in the interacting case than in a system
of $N$ independent protomers. Therefore, the coupling is an essential ingredient which enhances the sensitivity of the whole complex.

The conformational spread model is very reminiscent of the Ising model. In fact, if one associates to each protomer a spin variable $\sigma_i$ taking value $+1$ when the protomer is active ($\alpha_i = A$), or $-1$ when it is inactive ($\alpha_i = I$), one can represent the states of the system as $s = \{(\sigma_i, \ell_i)\}_{i=1}^N$ and the equilibrium properties of the model are determined by the Hamiltonian

$$H = -\frac{J}{2} \sum_{\langle i, j \rangle} \sigma_i \sigma_j - \sum_i h(\sigma_i, \ell_i),$$

where $J$ is a positive constant and $h$ is the single-protomer contribution, reproducing the energy diagram in figure 2,

$$h(\sigma, \ell) = \frac{1}{2} [\varepsilon_l - \varepsilon_A - (\varepsilon_{b}^{A}) - (\varepsilon_{b}^{b})] \sigma - \frac{1}{2} [\varepsilon_l + \varepsilon_A - (\varepsilon_{b}^{A}) + (\varepsilon_{b}^{b}) + 2\mu] \ell].$$

The one in equation (1) is an Ising Hamiltonian with ferromagnetic coupling $J$, where $h$ plays the role of an external local magnetic field, set by the occupation $\ell$; in equation (2), $\mu$ is the chemical potential, determined by the concentration of CheY-P, $c$, by

$$\mu = \mu_0 + \frac{1}{\beta} \ln \frac{c}{c_0},$$

where $\mu_0$ and $c_0$ are reference chemical potential and concentration, respectively. Hereafter, the notation $\sigma$ and $\alpha$ will be used interchangeably, according to the situation. The partition function $Z = \sum \exp(-\beta H(s))$ (where $\beta = 1/k_B T$ is the inverse temperature and the sum is done over the $4^N$ possible states of the ring of protomers) has been calculated exactly via a transfer matrix approach [15]. The analytic results found therein fit the experimental curves [3] of the ligand occupancy (average fraction of bound protomers) and the activity (fraction of protomers in the $A$ state) as a function of the concentration of CheY-P very well.

If on one hand the equilibrium properties of the conformational spread model are exactly known, on the other hand a full-fledged analytic treatment of the stochastic dynamics of this model seems difficult. In the definition of the conformational spread model given above, there is no prescription about the dynamics. A natural choice which satisfies detailed balance is the Glauber-like [12] Markovian dynamics, used in numerical simulations of this model in [13, 14]. In such prescription, the process $\{S_t\}$ which accounts for the kinetics of the conformational spread model is governed by the master (Kolmogorov) equation

$$\frac{\partial}{\partial t} P(s, t) = \sum_{s'} \{P(s', t) K(s' \rightarrow s) - P(s, t) K(s \rightarrow s')\},$$

where $P(s, t) = \text{Prob}\{S_t = s\}$ and $K$ are the rates defined as
From conformational spread to allosteric and cooperative models of \textit{E. coli} flagellar motor

\[
K(s \rightarrow s') = \left\{ \frac{\omega_f}{1 - \gamma} \left( 1 - \gamma \sigma_i \sigma_{i+1} + \sigma_{i-1} \right) \right\} e^{\beta \left( h\left(\sigma_i, \ell_i\right) \delta_{\ell_i', \ell_i} - \sigma_i \delta_{\ell_i', \ell_i} \right)} + \right. \\
+ \left. \omega_s e^{\beta \left( h\left(\sigma_i, 1-\ell_i\right) \delta_{\ell_i', \sigma_i} - \sigma_i \delta_{\ell_i', \sigma_i} \right)} \prod_{j \neq i} \delta_{\ell_j', \ell_j} \delta_{\ell_j', \ell_j} \right\} \prod_{j \neq i} \delta_{\ell_j', \ell_j} \delta_{\ell_j', \ell_j},
\]  

(5)

where the product of Kronecker $\delta$ indicates that the rates $K$ only involve one protomer at a time. Each term in equation (5) is obtained from detailed balance up to multiplicative factors $\omega_f$ and $\omega_s$; these constants account for typical timescales of the flipping and binding processes respectively. The constant $\gamma$ in the spin-flip contribution is set by the strength of the coupling, $\gamma = \tanh(\beta J)$. For a system made of a one protomer (or for a single protomer in absence of interaction, $\gamma = 0$), according to equation (5), we define the constants $k_a$ and $k_i$ as the rates for activation and inactivation with $\ell = 0$,

\[
k_a = \omega_f e^{-\beta \varepsilon_a}, \quad \text{and} \quad k_i = \omega_f e^{-\beta \varepsilon_i};
\]  

(6)

their counterparts for $\ell = 1$ are

\[
k_a \frac{c}{K_a} \quad \text{and} \quad k_i \frac{c}{K_i}.
\]  

(7)

The rates of binding and unbinding are respectively given by

\[
c k_b^\alpha = \frac{c}{K_b^\alpha} \omega_i e^{-\beta \varepsilon_i} \quad \text{and} \quad k_u^\alpha = \omega_s e^{-\beta \varepsilon_i},
\]  

(8)

when it is in the activity state $\alpha$. The ratio between the rate constants $k_u^\alpha/k_b^\alpha$ is the \textit{dissociation constant} of the binding process, $K_d^\alpha$:

\[
K_d^\alpha = \frac{k_u^\alpha}{k_b^\alpha} = c_0 e^{-\beta (\varepsilon_i^{(\alpha)} + \mu_0)}.
\]  

(9)

The dynamics of a single isolated protomer is depicted in figure 3. The ratios of the rate constants $k_{u,b}^\alpha$ and $k_{i,a}$ are determined by the equilibrium statistics, while their specific values affect the kinetics.

It is worth remarking that the binding/unbinding rates at one protomer only depend on the state of the protomer itself and no other protomer in the ring: this assumption of independent binding is typical of allosteric models.

Deriving an exact solution for the conditional probability $P(s, t|s_0, 0)$ by directly attacking the Kolmogorov equation (4) is far from being an easy task. However, as experiments show [13], in the flagellar motor regulation mechanism of \textit{E. coli} it is possible to identify a hierarchy of widely separated timescales. This opens up the possibility of operating a reduction of the set of states by gradually \textit{integrating out}/decimating fast degrees of freedom, operating a \textit{quasi-stationary} approximation: the timescale of the slow degrees of freedom is much longer than the time needed for the fast variables to relax to a stationary distribution; hence, the fast degrees of freedom enter the slow dynamics only through quantities averaged over such a stationary distribution (conditioned to the state of the slow variables) [16–18]. The application of such techniques to the study of the allosteric regulation of the motor of \textit{E. coli} will be the subject of the following sections. The approximation scheme is depicted in figure 4."
3. From the conformational spread to the MWC model

In the present problem, the fastest degrees of freedom are associated with the spin-activity variables: the (concerted) conformational transition between CW and CCW state is much faster than the timescale for binding/unbinding of CheY-P, respectively.
From conformational spread to allosteric and cooperative models of *E. coli* flagellar motor

occurring on typical times of $10^{-3}$ s and $10^{-1}$ s. In the associated Glauber dynamics in equation (5), this can be encoded in the limit $\omega_f \gg \gamma$. Furthermore, it can be seen that the coarsening dynamics of the spin-activity variables occurs over timescales much shorter than the typical time interval between two successive nucleations of an activity domain, the latter setting the frequency of the switch from CW to CCW and vice versa, while the binding $\{\ell_i\}$ is fixed. This is due to the strong coupling between the neighbouring protomers, $\beta J \gg 1$, or equivalently, $\gamma \to 1$. In this limit, the transition rates away from the fully aligned configurations (all $\sigma_i$ equal) are of order $\omega_f/(1 - \gamma)$, while all other spin transitions are much slower, with typical rate $\omega_f \ll \omega_f/(1 - \gamma)$.

The discussion of this latter time-scale separation is the subject matter of this section: it will be shown that the strong coupling limit amounts to considering the conformational spread model effectively equivalent to the MWC model, on the timescale of the switch. At the timescales typical of these fast processes, the binding state $\{\ell_i\}$ enters via a quenched external field term, playing a parametric role in determining the quasi-stationary distribution towards which the activity states relax. The slow binding dynamics will be discussed in the next section.

### 3.1. The role of the coupling

The ferromagnetic coupling in the conformational spread model is an essential ingredient which accounts for high sensitivity of the motor to the variation of concentration of CheY-P, due to the resulting cooperative response. The implementation of a large coupling $J$ is suggested by the experimental determination of this high sensitivity, quantified by a Hill coefficient $\sim 10$. As pointed out in [14], though, the estimation of the Hill coefficient does not impose severe constraints on the parameters of the model, especially on $J$; in fact, the numerical simulations performed therein show that the sensitivity depends more strongly on the activation energy of the single protomer ($\varepsilon_{A,i}$) than on the co-operativity. However, combining the experimental knowledge of the Hill coefficient with the information about other quantities, such as the mean locked state time and the mean switch time, Ma *et al* [14] were able to provide a very precise estimation of $J$, which is $\sim 4.5 k_B T$. For such a value of $J$ the formation of domain walls is strongly disfavored. At equilibrium, in fact, the ratio between the probability of configurations with $2m$ domains and the probability of a coherent one can be estimated as (see [11])

$$\frac{P(2m)}{P(0)} \sim \binom{N}{2m} \exp(-2m\beta J),$$  \hspace{1cm} (10)

where the binomial factor counts all possible ways of dividing $N$ protomers into $2m$ domains; for $N = 30 \gg 1$, the limit $P(2m) \ll P(0)$ corresponds to

$$\beta J > \log N \sim 3.5 = \beta J_*,$$  \hspace{1cm} (11)

satisfied by the estimate of $J$ performed in [14]. The stationary equilibrium configuration, at fixed binding states $\{\ell_i\}$, is therefore concentrated only on the two states with all the protomers in the same state. From a dynamical point of view, this means that states with one or several domain walls are just short-lived transients between coherent
Figure 5. Fast coarsening dynamics. Schematic representation of the fast rates of single-spin flipping $K_f$ for a system of four protomers. Grey boxes correspond to the states; periodic boundary conditions are understood. Arrows are drawn between two states (or groups of states) for which $K_f$ is non vanishing for some $i$. In particular: reversible transitions are allowed between states with equal number of domain walls; transitions to states with less domain walls are irreversible. Starting from any state, the dynamics leads to one of the coherent configurations in a time $\sim (1 - \gamma) \omega_f^{-1}$ (see equations (5) and (12)); such states are the only two activity states in the MWC allosteric model.

3.2. Decimation of fast variables

To realize the fast ‘emptying’ of configurations with several domain walls, it is necessary to analyse the structure of the transition rate matrix $K(s \rightarrow s')$, when the limits of the time-scale separation $(\omega \ll \omega_f \ll \omega_f/(1 - \gamma))$ are concerned.

In the limit $\gamma \rightarrow 1$, in fact, the non-vanishing entries of the matrix $K$, at frozen binding $\{\ell_i\}$, are either of order $\omega_f/(1 - \gamma)$, or of order $\omega_f$: the latter rates (slow) are defined for transitions consisting in a nucleation of a domain, i.e. creation of pairs of domain walls, and are denoted by $K_s$; the former (fast) are defined for all other transitions, i.e. motion and destruction of domain walls, and are denoted by $K_f$. We can therefore write $K = K_f + K_s$, with

$$K_f(s \rightarrow s') = K(s \rightarrow s') (1 - \delta_{\sigma_1 \ldots \sigma_N}) \sim \frac{\omega_f}{1 - \gamma},$$

(12)

and

$$K_s(s \rightarrow s') = K(s \rightarrow s') \delta_{\sigma_1 \ldots \sigma_N} \sim \omega_f,$$

(13)

where $K$ are defined in equation (5), and $\delta_{\sigma_1 \ldots \sigma_N}$ indicates that the spin-activity variables in $s$ have all the same value. One notices that the coherent configurations (all protomers active or inactive) are the only absorbing states of the fast process, since in such cases the entries of $K_f$ vanish. The dynamics specified by $K_f$ forbids the creation of pairs of domain walls and only allows translation or absorption of domain walls.
As a result, the fast dynamics leads to one or the other coherent configuration with a
typical rate $\omega_1/(1 - \gamma)$. As an explicative example, the case of $N = 4$ is depicted in
figure 5. On a timescale set by $1/\omega_1$, the nucleation of an activity domain can occur. In the
coherent activity configurations, the process involving the spin-activity variables has slow rates $K_c$. It is then possible to apply the standard techniques of time-scale separation \cite{16–18}, eliminating incoherent activity configurations from the dynamics at timescales comparable with $1/\omega_1$ or longer. The net effect of the fast coarsening dynamics is included in an effective way into rates, denoted by $K_c$, which provide the description of the dynamics at the nucleation timescale: a concerted transition between the two coherent configurations $I$ (all protomers inactive, $\sigma = -1$) and $A$ (all active, $\sigma = 1$), besides slow binding processes. In this model, the $N$-protomer complex can be in two different activity states, each of which present in $2^N$ binding configurations (two for each protomer): therefore, the model contains $2 \times 2^N$ states, and corresponds to the concerted allosteric MWC model \cite{6, 7}.

The structure of the state diagram of the MWC model with its rates $K_c$ is depicted in figure 6. In the appendix, the decimation procedure leading from the conformational spread to the MWC model, in the case of $N = 2$ has been worked out exactly. In general, the rate of a concerted switch from the activity state $\alpha = I$ (or $A$) to $\alpha' = A$ (or $I$) is

$$K_c(\alpha \to \alpha', \{\ell_i\}) = \sum_{j=1}^{N} K_c(\alpha \to \alpha^{(j)}, \{\ell_j\}) P_{\text{abs}}^{(j)}(\alpha'),$$ (14)
where $\alpha^{(j)}$ denotes the state where all the spins but the $j$th are in the state $\alpha$, and $P^{(j)}_{\text{abs}}(\alpha')$ is the probability of absorption in the state $\alpha'$ conditioned to the initial state $\alpha^{(j)}$.

A direct analytic derivation of the rates $K_c$ (or the probabilities $P^{(j)}_{\text{abs}}$) for a generic $N$-protomer ring can be extremely complicated. However, in the time-scale separation assumptions, the fast dynamics after the nucleation of an activity domain from a coherent state reaches one of its two absorbing states before another nucleation could possibly occur. This means that a calculation of the effective activity switching rates in the MWC model does not require the inclusion of all the incoherent states, but only those with just two domain walls: the coarsening process can be seen as the expansion or contraction of the domain which has been nucleated. The nucleated domain can either expand until it invades the whole ring (complete switch), or be ‘absorbed’ back (failed attempts).

Since the detailed balance is still respected by the rates in the decimated dynamics, all their pairwise ratios are fixed by the equilibrium distribution. Hence, since the equilibrium distribution of the MWC model is known from the Hamiltonian (1) (where the coupling part is just a constant term), it is sufficient to determine only one effective rate $K_c$ exactly. In the case where $\ell_i = 0$ for all protomers, one is able to calculate the rate of switching from the $I$ to the $A$ state, by mapping the coarsening process into a simple birth and death process, the random variable being the size of the domain with active protomers (see the appendix).

Regarding the binding process, the rate $K_c$ is just the binding/unbinding contribution in the rates $K$, defined in equation (5).

Although the dynamics of the MWC model depends on the detailed binding configuration $\{\ell_i\}$ in a highly non-trivial way, the equilibrium distribution depends on the total occupancy $l = \sum \ell_i$ only,

$$P_{\text{eq}}(I, l) = \frac{\left(\frac{c}{K^I_c}\right)^l N!}{\left(1 + \frac{c}{K^I_c}\right)^N + L^{-1}(1 + \frac{c}{K^A_c})^N}$$  \hspace{1cm} (15)

$$P_{\text{eq}}(A, l) = \frac{L^{-1}\left(\frac{c}{K^A_c}\right)^l N!}{\left(1 + \frac{c}{K^I_c}\right)^N + L^{-1}\left(1 + \frac{c}{K^A_c}\right)^N}$$  \hspace{1cm} (16)

where $L$ is the allosteric constant of the $N$-protomer MWC molecule,

$$L = \left(\frac{k_i}{k_a}\right)^N = e^{\beta(\epsilon_A - \epsilon_I)N}.$$  \hspace{1cm} (17)

There is an important comment to be made about the equilibrium distribution of the MWC model, specifically about the marginal probability for the active state, defined as the activity of the MWC molecule,
From conformational spread to allosteric and cooperative models of *E. coli* flagellar motor

\[
P_{eq}(A) = \sum_{l=0}^{N} P_{eq}(l, A) = \frac{1}{1 + L \left( \frac{K_d}{K_f} \right)^N \left( \frac{c + K_d}{c + K_f} \right)^N}.
\]  

In our problem, this corresponds to the CW bias of the flagellar motor, which is a function of the CheY-P concentration \( c \). In order for the MWC molecule to be a good allosteric switch, it needs to be almost certainly active for high enough concentration \( c \) and, vice versa, inactive when \( c \) is low:

\[
P_{eq}(A) \sim \begin{cases} 
(1 + L)^{-1} \to 0 & \text{for } c \to 0 \\
1 + L^{-1} \left( \frac{K_d}{K_f} \right)^N & \to 1 & \text{for } c \to \infty.
\end{cases}
\]

These limits impose the following constraints:

\[
1 \ll L \ll \left( \frac{K_d}{K_f} \right)^N.
\]  

Since the single protomer has higher ligand affinity (smaller dissociation constant \( K_d \)) when in the active state than in the inactive one, it is required that \( K_d^A < K_f^I \). From this last relation one realizes that the number of protomers sets the sensitivity of the switch: since \( K_d^I > K_d^A \), the larger \( N \), the larger the r.h.s. of the condition given by equation (19). Incidentally, depending on environmental stimuli *E. coli* is able to regulate the number of protomers of the flagellar motor [19–21].

4. From MWC to a cooperative binding model

As we already said at the beginning of section 3, the binding is much slower than the switching dynamics. We can assume that on the timescale at which one of the protomers binds or releases a CheY-P (set by a typical time \( \tau_b \sim 10^{-1} \) s), the activity of the ring safely reaches the equilibrium configuration, conditioned to the (quasi-static) value of \( k \):

\[
P_{eq}(l|l) = \frac{P_{eq}(l, I)}{P_{eq}(l)} = \frac{P_{eq}(l, I)}{P_{eq}(l, I) + P_{eq}(l, A)} = \frac{1}{1 + L^{-1} \left( \frac{K_d}{K_f} \right)^l},
\]

\[
P_{eq}(A|l) = \frac{P_{eq}(l, A)}{P_{eq}(l)} = \frac{P_{eq}(l, A)}{P_{eq}(l, I) + P_{eq}(l, A)} = \frac{1}{1 + L \left( \frac{K_d}{K_f} \right)^l}.
\]

Then, on timescales comparable to (or larger than) \( \tau_b \), the relevant dynamics is essentially the slow binding/unbinding one, while the fast activation/inactivation dynamics
From conformational spread to allosteric and cooperative models of E. coli flagellar motor

is averaged over the equilibrium conditional probabilities in equations (20) and (21), to give the effective rates $\bar{K}$ for the variable $l$:

$$\bar{K}(l \rightarrow l') = \sum_{\alpha \in \{A, I\}} P_{eq}(\alpha | l) K(l \rightarrow l', \alpha \rightarrow \alpha).$$

(22)

This averaging procedure is guaranteed to give an effective dynamics of the slow variables which still enjoys the Markov property. The effective binding/unbinding rates of the whole allosteric complex are, in fact,

$$\bar{K}(l \rightarrow l + 1) = (N - l) c \tilde{k}_b^{(l)} \equiv b_l,$$

$$\bar{K}(l \rightarrow l - 1) = l \tilde{k}_u^{(l)} \equiv u_l,$$

(23)

where

$$\tilde{k}_b^{(l)} = \frac{k_{b,u}^A}{1 + L \left( \frac{K_d^A}{K_a} \right)^l} + \frac{k_{b,u}^I}{1 + L^{-1} \left( \frac{K_d^I}{K_a} \right)^l},$$

(24)

depending only on the current value of $l$.

A comment about the range of validity of this result is in order: for the time-scale separation to hold, the rates $\bar{K}$ must be small enough to guarantee that the binding/unbinding process is still much slower than the activation/inactivation. In particular, this implies that the concentration of ligands in the environment $c$ cannot be exceedingly large; thus, in the time-scale separation approximation, we keep ourselves far from this regime.

The reduced system is also a Markov process, governed by the following master equation:

$$\partial_t P_l(t) = b_{l-1} P_{l-1}(t) + u_{l+1} P_{l+1}(t) - [b_l + u_l] P_l(t).$$

(25)

The process hence obtained is a birth-and-death process, restricted on the set of integers between $l = 0$ and $l = N$. These extremes are reflecting boundary states. This dynamics eventually leads to the equilibrium state $P_{eq}(l)$, easily calculated by marginalizing the joint probability distribution $P_{eq}(\alpha, l)$, given in equations (15) and (16):

$$P_{eq}(l) = P_{eq}(A, l) + P_{eq}(I, l).$$

(26)

Albeit much reduced, this model still encodes a lot of information about the actual dynamics of the switch. Indeed, the flagellar motor switch is triggered by the number of ligands bound to the allosteric complex. In the next section we present a numerical analysis of the dynamical properties of the effective cooperative binding model obtained above.

5. Dynamics of the effective cooperative binding model

In this section we analyze the case of a motor constituted by $N = 30$ Fli molecules. The allosteric constant $L$ and the dissociation constants $K_d^A$ and $K_d^I$ have been chosen consistently with [2] and works cited therein: $L = 10^7$, $K_d^A = 1.84 \mu M$ and $K_d^I = 5.52 \mu M$;

doi:10.1088/1742-5468/aa569e
these values provide a qualitatively good fit of the activity as a function of the CheY-P concentration $c$ (see figure 7). With this choice of the parameters, we can easily see that the bound in equation (19) is safely satisfied, so that the motor displays a switch behaviour, manifest in the response curve in figure 7. One also notices that the motor operates within a range of concentration $c$ roughly between $K_d^A$ and $K_d^I$. The maximum sensitivity is found around a value $c_*$, which correspond to a CheY-P concentration such that the CW (active) and the CCW (inactive) states occur with equal probabilities at equilibrium.

As already remarked above, the specific values of the rate constants $k_{h,u}^A$ are irrelevant for the equilibrium properties of the model, but they determine the characteristic timescale for the motor switch. Out of these four constants, only two are actually independent, since we have already defined their ratios $K_d^A = k_d^A/k_b^A$ and, analogously, $K_d^I = k_d^I/k_b^I$. Thus, the dynamics of the cooperative binding model can be specified by only the parameters $k_b^I$ and $k_b^A$; the qualitative behaviour is determined only by their ratio, while their specific values give information about the overall timescale (of the binding process). In our work, we set $k_b^A = 2.8 \text{ s}^{-1}$ and $k_b^I = 5.0 \text{ s}^{-1}$, consistently with those recommended by Bai et al [13].

As previously discussed, the cooperative binding model obtained so far must provide an accurate description of the statistics of slow observables, specifically those which vary over timescales typical of the binding process or longer. From experimental results, it is clear that the mean locked-state time (i.e. the time in which the motor

**Figure 7.** Activity and mean Fli occupancy at equilibrium. Analytic results for $R_\text{eq}(A)$ (solid blue line) and mean Fli relative occupancy $\langle b/N \rangle$ (dashed red line) as a function of the CheY-P concentration, $c$. The dots are the experimental results presented in [2]. In our work we chose the dissociation constants to be $K_d^A = 1.84 \mu M$ and $K_d^I = 5.52 \mu M$, respectively, while the allosteric constant has been set to be $L = 10^7$. The plot shows the effect of allostery: the activity response is much more sensitive than the binding to changes of concentration of CheY-P.
stays in a certain rotational state between two consecutive switches) is such an observable; we show, indeed, that the cooperative binding model captures its statistics very well.

Let us denote by \( \bar{l}_I \) and \( \bar{l}_A \) the averages of the occupancy \( l \) conditioned, respectively, to the inactive state (CCW) and active state (CW). One can see that the probability of the CW state is very close to unity if the Fli occupancy is conditioned to \( \bar{l}_A \), and almost vanishing when conditioned to \( \bar{l}_I \) (figure 8). Therefore, since the fast activity variables are slaved to the slow binding ones, we can state that a good measure of the locked-state time is the first passage time between \( \bar{l}_A \) and \( \bar{l}_I \).

Let us then study the first arrival time at \( \bar{l} \) from a generic state \( k \). If we denote by \( f_k \) the probability density function of this time interval, its moment generating function

\[
g_k(\lambda) = \int_0^\infty d\tau \ e^{-\lambda \tau} f_k(\tau),
\]

satisfies

\[
\sum_l g_l(\lambda) (M_{l,k} - \lambda \delta_{l,k}) = -\delta_{k,l},
\]

where \( M \) is the generator of the process in which absorbing conditions have been put at \( \bar{l} \). From equation (28), we can derive the equation for the mean first passage time at \( \bar{l} \), using \( \langle \tau_l \rangle = g'_k(\lambda)|_{\lambda=0} \):

\[
\sum_l \langle \tau_l \rangle M_{l,k} = -1.
\]

Exact results are obtained by inverting equation (29) and are shown in figure 9, with \( k = \bar{l}_i \) and \( \bar{l} = \bar{l}_a \), and vice versa, for several values of the bias \( P_{eq}(A) \).

**Figure 8.** Motor switch ruled by the cooperative binding. On the left, the probability of the CW state conditioned on the Fli occupancy; for values of \( l \) fixed in the shaded regions, the motor is in the CW or CCW state with 95% probability. On the right, average occupancy as a function of the CW bias: the dashed line corresponds to the unconditional average (see also figure 7) while the solid lines represent the averages conditioned to the CW state (red), \( \bar{l}_A \), and CCW state (blue), \( \bar{l}_I \). The values of \( \bar{l}_A \) and \( \bar{l}_I \) lie in the respective 95%-confidence intervals, with a CW bias between \( \approx 0.1 \) and \( \approx 0.9 \). The locked–state time can be interpreted as the first passage time between \( \bar{l}_A \) and \( \bar{l}_I \) in the cooperative binding model.
We also extract the probability density by solving equation (28) and numerically performing the inverse Laplace transform. The resulting distribution is very similar to the experimental and numerical results presented in [13] and [14], confirming that the effective cooperative binding model gives an excellent description of the motor kinetics.

6. Discussion

In this work we have pursued an analytic approach to the description of the dynamics of the conformational spread model, a phenomenological model which reproduces well the allosteric regulation of the flagellar motor in E. coli. Our analysis was based on the existence of a hierarchy of widely separated timescales in the biochemistry of the motor of E. coli. Specifically, over the scale of conformational transitions between CW and CCW states in the Fli molecules (protomers, constituents of the flagellar motor) incoherent states are very short-lived, and only coherent states of activity are sufficiently long-lived. In such a limit we have reduced the conformational spread to the well known Monod–Wyman–Changeux model. For a motor with $N = 30$ protomers, this approximation amounts to reducing the number of states in the model from $4^N \sim 10^{18}$ to $2(N + 1) = 62$.

Moreover, the binding of CheY-P to the Fli molecules occurs much less frequently than the switch from a completely active to inactive state, allowing the fast activity states under quasi-stationary Fli occupancy (number of CheY-P bound to the motor) to be averaged out. This allowed reducing the number of states further and getting a cooperative binding model containing only $N + 1 = 31$ states—the possible values of

doi:10.1088/1742-5468/aa569e
From conformational spread to allosteric and cooperative models of *E. coli* flagellar motor

...the overall occupancy. The resulting Markov process is a birth-and-death process which can be studied semi-analytically, with virtually no computational cost.

This effective model for the slow variables is able to capture the dynamics of observables varying on timescales of $10^{-1}$ s or longer. Two such observables are the CW and CCW locked-state time, which correspond to the duration of tumbles and runs, respectively, with timescales typically of the order of seconds. We have showed that our model reproduces the statistics of the locked state time and is in extremely good quantitative agreement with experimental measurements.

In perspective, our approach could be extended to include the even slower kinetics of motor remodeling. Indeed, it is known that over timescales much longer than the binding times (typically minutes), *E. coli* is also able to modify the flagellar motors by changing the number of Fli molecules, i.e. the protomers \[19, 20\]. This mechanism provides an adaptation layer at the output and restores the sensitivity of the motor when CheY-P concentration are kept outside the dynamic range for a long time \[21\].

Finally, experimental work on flagellar motors in *Vibrio alginolyticus* \[22\] has shown a nontrivial locked-state time-statistics. The techniques exploited in our work might prove useful in addressing theoretically the origin of these observations.

**Acknowledgments**

We are grateful to Stefano Bo for illuminating insights and discussions.
Appendix. Decimation of the fast coarsening dynamics in the conformational spread

In this appendix we show that the decimation of the short-living incoherent states in the Glauber-like dynamics of conformational spread model leads to the MWC model, in which the rates generally depend on the full binding state \( \{ \ell_i \}_{i=1}^N \) (kept frozen at this step). Nevertheless, the equilibrium properties of the resulting Markovian model only depend on the global variable \( l = \sum \ell_i \).

For the sake of simplicity, we will describe in detail the case of \( N = 2 \). In the case of generic \( N \), and in the limit of large coupling, we compute exactly the probability of completion of the switch after the nucleation of one domain, when all the protomers are unbound (\( \ell_i = 0 \)): this provides information about the overall timescale of the concerted switching process; the switching rates in presence of a generic occupation can be then obtained from this by means of the detailed balance condition.

A.1. Coarsening with 2 protomers

At frozen binding, the dynamics of the activity variables is equivalent to the one of \( N \) spins with nearest-neighbour ferromagnetic interaction with strength \( J \), subjected to a ‘magnetic field’ given by equation (2):

\[
\beta h(\sigma_i, \ell_i) = h_i \sigma - \lambda_i,
\]

(A.1)

where

\[
h_i = \frac{\beta}{2} [\varepsilon_f - \varepsilon_A - (\varepsilon_b^{(1)} - \varepsilon_b^{(2)})\ell_i], \quad \lambda_i = \frac{\beta}{2} [\varepsilon_f + \varepsilon_A - (\varepsilon_b^A + \varepsilon_b^f + 2\mu)\ell_i].
\]

(A.2)

According to equation (5), and to the considerations given in section 3, neglecting the binding dynamics, we can decompose the full matrix of the rates \( K \), when \( \gamma \to 1 \), as the sum the fast contribution \( K_f \)

\[
K_f = \omega f \left( \frac{1 + \gamma}{1 - \gamma} \right) \begin{pmatrix}
0 & e^{h_2 - \lambda_2} & e^{h_1 - \lambda_1} & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & e^{-h_1 - \lambda_1} & e^{-h_2 - \lambda_2} & 0
\end{pmatrix},
\]

(A.3)

and a slow part \( K_s \),

\[
K_s = \omega s \begin{pmatrix}
0 & 0 & 0 & 0 \\
e^{-h_2 - \lambda_2} & 0 & 0 & e^{h_1 - \lambda_1} \\
e^{-h_1 - \lambda_1} & 0 & 0 & e^{h_2 - \lambda_2} \\
0 & 0 & 0 & 0
\end{pmatrix},
\]

(A.4)

where the row and column index respectively correspond to the final and initial states, labelled as in figure A1. We note that the fast dynamics has two absorbing states, which are the equilibrium configurations in the time-scale separation limit: these states are the coherent configurations, i.e. those with all the protomers in the same activity state (all spins aligned).
On the slow timescales (much longer than the coarsening process but much shorter than the binding), we can calculate effective rates of passing from one coherent state to the other, given by equation (14). These rates are limited by the rate of flipping one spin from the starting coherent configuration: this is a slow process, since such transition costs an energy $\sim J \gg \beta$. The rates are then affected by the probabilities that, once this flip has occurred, the process reaches the other coherent state and is not absorbed back in the starting coherent state: such probabilities are completely determined by the fast dynamics. The difficulty in calculating such probability stems from the fact that, for a generic number of protomers $N$, a huge number of paths contributes, with amplitudes strongly dependent on the binding configuration $\{\ell_i\}$. The general way of proceeding is presented in [16–18].

In the simple example where $N=2$, there are only two paths which give contribution to the concerted transition: the flip of the first spin followed by the flip of the second, or the flip of the second followed by the flip of the first. Summing up the rates of these possible channels yields the effective rates of the concerted switch$^3$:

$$K_c(I \to A) = K_c(\downarrow\downarrow\to\uparrow\uparrow) \frac{K_f(\uparrow\downarrow\to\uparrow\uparrow)}{K_f(\uparrow\downarrow\to\downarrow\downarrow) + K_f(\uparrow\downarrow\to\uparrow\uparrow)}$$

$$+ \; K_c(\downarrow\downarrow\to\uparrow\uparrow) \frac{K_f(\downarrow\uparrow\to\uparrow\uparrow)}{K_f(\downarrow\uparrow\to\downarrow\downarrow) + K_f(\uparrow\downarrow\to\downarrow\downarrow)}.$$  \hspace{1cm} (A.5)

and

$$K_c(A \to I) = K_c(\uparrow\uparrow\to\downarrow\downarrow) \frac{K_f(\uparrow\downarrow\to\downarrow\downarrow) + K_f(\uparrow\downarrow\to\uparrow\uparrow)}{K_f(\uparrow\downarrow\to\downarrow\downarrow) + K_f(\downarrow\uparrow\to\uparrow\uparrow)}$$

$$+ \; K_c(\uparrow\uparrow\to\downarrow\downarrow) \frac{K_f(\uparrow\downarrow\to\downarrow\downarrow) + K_f(\uparrow\downarrow\to\uparrow\uparrow)}{K_f(\uparrow\downarrow\to\downarrow\downarrow) + K_f(\downarrow\uparrow\to\uparrow\uparrow)}.$$  \hspace{1cm} (A.6)

By substituting equations (12) and (13) into these expressions, we find

$$K_c(A \to I, \{\ell_i\}) = \omega_f \left\{ \frac{e^{-h_1-\lambda_1}}{1 + e^{(h_1+h_2-\lambda_1+\lambda_2)}} + \frac{e^{-h_2-\lambda_2}}{1 + e^{(h_1+h_2-\lambda_1+\lambda_2)}} \right\}$$  \hspace{1cm} (A.7)

and

$$K_c(I \to A, \{\ell_i\}) = \omega_f \left\{ \frac{e^{h_1-\lambda_1}}{1 + e^{-(h_1+h_2)-\lambda_1+\lambda_2}} + \frac{e^{h_2-\lambda_2}}{1 + e^{-(h_1+h_2)-\lambda_1+\lambda_2}} \right\}.$$  \hspace{1cm} (A.8)

Even in this simple case with two protomers, the first time-scale separation yields effective rates which depend on the full binding state in a non trivial way, and not only on the sum $l = \sum \ell_i$.

However, detailed balance being preserved by the coarse-graining procedure, we have

$^3$ The parametric dependence of the rates on the binding state $\{\ell_i\}$ is understood, but not made explicit in the notation.
From conformational spread to allosteric and cooperative models of *E. coli* flagellar motor

\[
\frac{K_c(A \rightarrow I, \{\ell_i\})}{K_c(I \rightarrow A, \{\ell_i\})} = \frac{P_{eq}(I|\{\ell_i\})}{P_{eq}(A|\{\ell_i\})} = e^{-2(h^1 + h^2)},
\]

(A.9)

consistently with the general formula\(^4\)

\[
P_{eq}(\sigma|\{\ell_i\}) = \frac{1}{Z(\{\ell_i\})} e^{\sum_i h_i^c},
\]

(A.10)

which gives the Boltzmann weights according to the Hamiltonian (1) restricted to the coherent configuration (in which case the coupling term is a constant contribution cancelled by the normalization \(Z\)). From equation (A.1), it is obvious that such Boltzmann weights only depend on the global occupancy \(l = \sum \ell_i\).

### A.2. \(N\)-protomer, completely unbound case

In the general case with \(N\) protomers, all unbound\(^5\), we are able to map the coarsening process into a simple birth–and–death process which, in the limit \(\gamma \rightarrow 1\), has site-independent rates. First of all, as we remarked in the main text, because of the time-scale separation, the fast coarsening process does not involve any state but the coherent (which are the long-living states) and the ones with only two domain walls. Then, the coarsening is simply a motion of the domain walls, namely an expansion or contraction of the domain which has been nucleated, until one of the coherent states is reached. The expansion/contraction of this domain can happen by a flip of a spin at its right or left border: if the protomer occupancy \(\ell\) is the same for all sites, it is not important at which side of the domain the expansion/contraction occurs. Therefore, we can label the states visited by the coarsening process just by the number of protomers in e.g. the active state (spin up), denoted by \(n\): far from the absorbing states \(n = 0\) and \(n = N\), the rate of increasing or decreasing the number of active protomers is twice the rate of moving a domain wall; the absorption rates from the state \(n = 1\) and \(n = N - 1\) are the rates of absorbing the two domain walls. The process is schematically represented here,

\[
\begin{array}{cccccc}
0 & \overset{\omega_f}{\longrightarrow} & 1 & \cdots & \overset{\omega_f}{\longrightarrow} & n \\
\omega_f \frac{\epsilon_{\ell}}{1 - \gamma} & \longrightarrow & e^{-h} & \cdots & \longrightarrow & \frac{\epsilon_{\ell}}{1 - \gamma} e^{-h} \\
& & \omega_f \frac{\epsilon_{\ell}}{1 - \gamma} e^{-h} & \cdots & \omega_f \frac{\epsilon_{\ell}}{1 - \gamma} & \longrightarrow \\
& & \omega_f \frac{\epsilon_{\ell}}{1 - \gamma} e^{-h} & \cdots & \omega_f \frac{\epsilon_{\ell}}{1 - \gamma} & \longrightarrow \\
n + 1 & \overset{\omega_f}{\longrightarrow} & \cdots & \overset{\omega_f}{\longrightarrow} & N - 1 & \overset{\omega_f}{\longrightarrow} \\
& & \omega_f \frac{\epsilon_{\ell}}{1 - \gamma} e^{-h} & \cdots & \omega_f \frac{\epsilon_{\ell}}{1 - \gamma} & \longrightarrow \\
N & & & & & \omega_f \frac{\epsilon_{\ell}}{1 - \gamma} e^{-h}
\end{array}
\]

where the (reduced) magnetic field \(h\) is the value of \(h_i\) given by equation (A.2) specified to \(\ell_i = 0\), so

\[
h = \frac{\beta}{2}(\varepsilon_{\ell} - \varepsilon_A);\]

such (negative) value is responsible for the downward alignment of the spin-activity variables, favouring the inactive state. The solid arrows represent the fast rates, while the dashed ones are the slow rates of nucleation of one domain.

In the strong-coupling limit, \(\gamma \rightarrow 1\), and all the fast rates are asymptotically equal; the coarsening dynamics is then formally described by a birth-and-death process with site-independent rates, defined on the integer numbers between 0 and \(N\), i.e. as asymmetric

\(^4\) The spin variable \(\sigma\) in this expression corresponds to the spin-activity variable of the whole coherent system.

\(^5\) In general, with all the protomers with the same occupancy.
random walk with absorbing boundary conditions. The probability of being absorbed in state \( N \), starting from state 1, is easily calculated to be

\[
P_{\text{abs}}(N \mid 1) = e^h(N-1) \frac{\sinh h}{\sinh Nh}. \tag{A.11}
\]

Once multiplied by the slow exit rate from 0 to 1, this gives the effective rate of switching from the inactive to the active state, in absence of ligands:

\[
K_s(I \to A, \{\ell_i = 0\}) = N \omega_f e^hN \frac{\sinh h}{\sinh Nh} = N \omega_f L^{-1/2} \frac{\sinh h}{\sinh Nh}, \tag{A.12}
\]

where \( L \) is the allosteric constant of the \( N \)-protomers MWC molecule, defined in the main text as \( L = (k_i/k_a)^N = \exp N\beta(\epsilon_4 - \epsilon_I) \). Similarly, for the opposite switch, one has

\[
K_s(A \to I, \{\ell_i = 0\}) = N \omega_f e^{-hN} \frac{\sinh h}{\sinh Nh} = N \omega_f L^{1/2} \frac{\sinh h}{\sinh Nh}. \tag{A.13}
\]

These rates are exact up to a correction of order \( 1 - \gamma \), which is exponentially small in the coupling \( \beta J \) (see section 2). We notice that the ratio between these switching rates is the allosteric constant \( L \), as expected from the detailed balance condition and from the Hamiltonian (1). The one in equation (A.12), or, alternatively, equation (A.13), is the overall frequency scale of the switching dynamics in the MWC model. All the other switching rates are found from these ones by applying the detailed balance condition.

References

[1] Berg H C 2008 *E. coli in Motion* (Berlin: Springer)
[2] Berg H C 2003 The rotary motor of bacterial flagella Biochemistry 72 19
[3] Sourjik V and Berg H C 2002 Proc. Natl Acad. Sci. 99 12669
[4] Shi Y and Duke T 1998 Phys. Rev. E 58 6399
[5] Shimizu T S, Le Novère N, Levin M D, Beavil A J, Sutton B J and Bray D 2000 Nat. Cell Biol. 2 792
[6] Monod J, Wyman J and Changeux J-P 1965 J. Mol. Biol. 12 88
[7] Marzen S, Garcia H G and Phillips R 2013 J. Mol. Biol. 425 1433
[8] Eigen M 1967 Nobel Symp. 5 333
[9] Duke T A J and Bray D 1999 Proc. Natl Acad. Sci. 96 10104
[10] Alon U, Camarena L, Surette M G, y Arcas B A, Liu Y, Leibler S and Stock J B 1998 EMBO J. 17 4238
[11] Duke T A J, Le Novère N and Bray D 2001 J. Mol. Biol. 308 541
[12] Krapivsky P L, Redner S and Ben-Naim E 2010 A Kinetic View of Statistical Physics (Cambridge: Cambridge University Press)
[13] Bai F, Branch R W, Nicolau D V, Pilizota T, Steel B C, Maini P K and Berry R M 2010 Science 327 685
[14] Ma Q, Nicolau D V, Maini P K, Berry R M and Bai F 2012 PLoS Comput. Biol. 8 1002523
[15] Mohr S G J, Mack A H and Regan L 2010 Phys. Rev. E 82 031913
[16] Pavliotis G A and Stuart A 2008 Multiscale Methods: Averaging and Homogenization (Berlin: Springer)
[17] Weinan E 2011 Principles of Multiscale Modeling (Cambridge: Cambridge University Press)
[18] Bo S and Celani A 2016 Phys. Rep. (doi:10.1016/j.physrep.2016.12.003)
[19] Delalez N J, Wadhams G H, Rosser G, Xue Q, Brown M T, Dobbie I M, Berry R M, Leake M C and Armitage J P 2010 Proc. Natl Acad. Sci. 107 11347
[20] Lele P P, Branch R W, Nathan V and Berg H C 2012 Proc. Natl Acad. Sci. 109 20018
[21] Yuan J, Branch R W, Hosu B G and Berg H C 2012 Nature 484 233
[22] Xie L, Altindal T and Wu X-L 2015 PloS One 10 e0141654

doi:10.1088/1742-5468/aa569e