Enzymes are proteins that catalyze chemical reactions. The simplest, and most extensively studied, enzymatic reaction is

\[ E + S \xrightarrow{\omega_1} ES \xrightarrow{\omega_2} E + P \]  

(1)

where \( E \), \( S \) and \( P \) denote the enzyme, substrate and product, respectively. The rate \( V \) of the reaction in bulk was derived by Michaelis and Menten in a celebrated classic \cite{1} that marked its centenary last year \cite{2, 3}. A more general form of this rate \( V \), derived by Briggs and Haldane about a decade later \cite{4}, is now usually referred to as the Michaelis-Menten (MM) equation.

For a chemical reaction where a bulk of substrate is catalyzed by a single molecule of the corresponding enzyme \cite{5, 6}, rate is an ill-defined concept; instead the time taken by the enzyme for its successive turnovers is the prime quantity of interest. The statistical properties of the turnover is well characterized by the probability distribution of the turnover times (DTT). Deriving exact analytical expressions for this distribution, particularly its dependence on the substrate concentration \([S]\), has been one of the fundamental challenges in single-molecule enzymology. The distribution of dwell times (DDT) of a motor characterizes its stochastic alternating pause-and-translocation along a filamentous track. The DDT of a molecular motor is the analog of the DTT of the enzymes \cite{11, 12}. Although we use the terminology of ATPase (and use the specific notation [ATP] instead of the generic symbol \([S]\) for the substrate concentration), all the general conclusions drawn here remain equally valid for other enzymes with identical kinetic schemes.

The first two moments of DTT have been at the main focus of attention many recent works. The inverse of the mean turnover time \( \langle t \rangle \) is the average rate \( V \) of the reaction. Similarly the fluctuations in the turnover time is expressed by the randomness parameter \( r \) \cite{11}. In wide varieties of situations the mean turnover time \( \langle t \rangle \) has been found \cite{6, 13, 11} to obey the MM eqn.

\[ \frac{1}{V} = \langle t \rangle = \frac{1}{\omega_2} \left( 1 + \frac{K_M}{[ATP]} \right) \]  

(2)

where the Michaelis constant \( K_M \) is given by

\[ K_M = \frac{\omega_1 + \omega_2}{\omega_1} \]  

(3)

So far as the dependence of \( r \) on \([ATP]\) is concerned, an elegant expression reported in \cite{12} (see also refs. \cite{14, 13}), is given by \cite{11, 16}

\[ r = \frac{\langle t^2 \rangle - \langle t \rangle^2}{\langle t \rangle^2} = \left( 1 + \frac{[ATP]}{K_M} \right)^{-2} \left( \frac{1}{N_L} + \frac{2}{N_L N_S} \frac{[ATP]}{K_M} + \frac{1}{N_S} \left( \frac{[ATP]}{K_M} \right)^2 \right) \]  

(4)

which involves three parameters \( N_L, N_S \) and \( \alpha \); from now onwards, we’ll refer to eq. (4) as the MCB equation.

Although for an overwhelmingly large class of enzymatic reactions \( \langle t \rangle \) and \( r \) follow the general forms of
The kinetic scheme of our model is shown. The integers \( j - 1, j, j + 1 \ldots \) denote the spatial positions of the motor. At each spatial position the motor can exist in one of the two allowed “internal” states that are labelled by 1 and 2. The arrows and the associated symbols depict the allowed transitions and the corresponding rates. Note that in the limit \( \omega_b = 0 \) this scheme reduces to the MM kinetics provided one identifies states 1 and 2 with the substrate-free and substrate-bound states of the enzyme and the rates \( \omega_h, \omega_s, \omega_f \) with \( \omega_{-1}, \omega_{-2}, \omega_2 \) respectively, in equation (4).

The approximation (7) is valid if \( \omega_h \) is much larger than both \( \omega_s \) and \( \omega_f \). Small \( \omega_h \) helps in examining the connection with the limit \( \omega_b = 0 \). Moreover, since

\[
\omega_h = \omega_h^0 [ATP],
\]

where \( \omega_h^0 \) is independent of ATP concentration, large \( \omega_h \) corresponds to high concentration of ATP provided \( \omega_h^0 \) is not too small.

The full exact expression for \( \langle t \rangle \) for the kinetic scheme shown in fig. 1 is given by (10).
corresponding prediction of the exact expression \( \xi \). The higher is the value of \( M \), the better is the agreement with the exact result.

For a graphical test of the range of validity of the approximate expression (10) we plot the inverse of (t) (i.e., the average rate) in Fig.2 as a function of ATP concentration for a few different values of \( \omega_b \). Even with \( M \) as low as 4, the predictions of (10) are practically indistinguishable from those of (9), except at very low [ATP] (see the inset of Fig.3).

The exact expression for \( r \) in this model is (10)

\[
 r = \frac{2(2\omega_b + \omega_f)\omega_h\left[(2\omega_b + \omega_f)\omega_h - (2\omega_b + \omega_f + \omega_h + \omega_s)^2\right]}{(2\omega_b + \omega_f + \omega_h + \omega_s)^2\omega_b(2\omega_b + \omega_f + \omega_h - \omega_h) - \omega_f\omega_h - \omega_b\sqrt{(2\omega_b + \omega_f + \omega_h - \omega_h)^2 + 4\omega_h\omega_s}} - 1 \quad (11)
\]

In all the plots made above we used \( \omega_0^b = 10^7 \text{s}^{-1} \) per mole. But, for approximating (11) by an infinite series that correlates directly with eq. (4), we now also assume that \( \omega_h^0 \) is sufficiently small so that

\[
 [\text{ATP}] / \kappa \ll 1, \quad \text{in spite of high \ [ATP].} \quad (12)
\]

Under the approximations (4) eq. (11) reduces to

\[
 r = \left(1 + \frac{[\text{ATP}]}{\kappa}\right)^{-2} \sum_{n=0}^{\infty} \xi_n \left(\frac{[\text{ATP}]}{\kappa}\right)^n; \quad (13)
\]

the expressions for the first six coefficients \( \xi_n(n = 0, 1, \ldots, 5) \) are given in the appendix B. The series in eq. (13) converges rapidly because of the condition (12) and it reduces to eq. (4) for \( \omega_b = 0 \). Over physiologically relevant range of concentration of ATP, which hardly ever exceeds few mM, the expression (13) can yield highly accurate estimate of \( r \), as demonstrated by the graphical

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**FIG. 2**: (Color online) Average ATPase rate is plotted as a function of ATP concentration using inverse of the Eq.(5) (red), and Eq.(9) (dotted lines for \( M = 0 \)(Blue), 1(Magenta), 2(Grey), 3(Green), 4(Black)) for \( \omega_b = 1125 \text{s}^{-1} \). Other parameters are as follows: \( \omega_f = 55 \text{s}^{-1} \) and \( \omega_s = 145 \text{s}^{-1} \).

**FIG. 3**: (Color online) Average ATPase rates obtained from the exact expression (9) are plotted against [ATP] by continuous curves for \( \omega_b = 0 \) (red), \( \omega_b = 30 \text{s}^{-1} \) (blue), \( \omega_b = 50 \text{s}^{-1} \) (magenta) and \( \omega_b = 100 \text{s}^{-1} \) (green)). Black dotted lines for the respective \( \omega_b \) values are obtained from the approximated expression (10). Other parameters used for this plot are \( \omega_s = 145 \text{s}^{-1}, \omega_f = 55 \text{s}^{-1} \).

The exact expression for \( r \) in this model is (10)

\[
 r = \frac{2(2\omega_b + \omega_f)\omega_h\left[(2\omega_b + \omega_f)\omega_h - (2\omega_b + \omega_f + \omega_h + \omega_s)^2\right]}{(2\omega_b + \omega_f + \omega_h + \omega_s)^2\omega_b(2\omega_b + \omega_f + \omega_h - \omega_h) - \omega_f\omega_h - \omega_b\sqrt{(2\omega_b + \omega_f + \omega_h - \omega_h)^2 + 4\omega_h\omega_s}} - 1 \quad (11)
\]

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**FIG. 4**: (Color online) Randomness parameter evaluated from the approximate expression (10) for \( \omega_b = 1 \text{s}^{-1} \) is compared with the corresponding prediction of the exact expression (11) by plotting both against [ATP]. The other parameters used for this figure are \( \omega_s = 145 \text{s}^{-1}, \omega_f = 55 \text{s}^{-1} \), and \( \omega_0^b = 1000 \text{s}^{-1} \) per mole.
comparison with the corresponding exact result (11) in fig 4.

In almost all branches of physical sciences series expansion has been an extremely powerful tool for systematic approximation of important quantities. In the same spirit in this letter we have introduced series expansion method for analyzing stochastic kinetics in single-molecule enzymology and single-motor biophysics. We have also established the utility of these generalized MM and MCB equations (20) by comparing these with the corresponding exact results. The series expansion approach is expected to be very useful if exact analytical treatment is impossible because of the complexity of the network of pathways in the mechano-chemical kinetics of the system.

Appendix A: Coefficients of the series for \( t \)

\[
\xi_0 = -(1 - \gamma)^2, \quad (A1)
\]

\[
\xi_1 = 2\gamma(1 - \gamma)^2, \quad (A2)
\]

\[
\xi_2 = \gamma(2 - 5\gamma)(1 - \gamma)^2, \quad (A3)
\]

\[
\xi_3 = 2\gamma(1 - 6\gamma + 7\gamma^2)(1 - \gamma)^2, \quad (A4)
\]

\[
\xi_4 = \gamma \left( 2 + 5\gamma \left( \gamma \{ 20 + 7\gamma(4\gamma - 5) \} - 5 \right) \right) \quad (A5)
\]

where \( \gamma \) is given by eq. (6).

Appendix B: Coefficients of the series for \( r \)

\[
\xi_0 = \frac{4\omega_b + \omega_f + \omega_s}{\omega_f + \omega_s}, \quad (B1)
\]

\[
\xi_1 = \frac{2(2\omega_b\omega_f + \omega_s(\omega_f + \omega_s))}{(\omega_f + \omega_s)^2}, \quad (B2)
\]

\[
\xi_2 = \frac{16\omega_b^3\omega_f^2 + \omega_f(\omega_f + \omega_s)^4 + 2\omega_b(\omega_f + \omega_s)(4\omega_f + 5\omega_s)(\omega_f^2 + \omega_s^2) + 4\omega_b^2(5\omega_f^3 + 5\omega_f^2\omega_s + 3\omega_f\omega_s^2 + \omega_s^3)}{(2\omega_b + \omega_f)(\omega_f + \omega_s)^2(2\omega_b + \omega_f + \omega_s)}, \quad (B3)
\]

\[
\xi_3 = \frac{4\omega_b\omega_s}{(2\omega_b + \omega_f)(\omega_f + \omega_s)^2(2\omega_b + \omega_f + \omega_s)^2} \left[ -4\omega_f^2(3\omega_f + 2\omega_s)^2 - 2\omega_b(\omega_f + \omega_s)(3\omega_f + 2\omega_s)(3\omega_f^2 - 4\omega_s^2) \right.
\]

\[
\left. - 3(\omega_f + \omega_s)^3(\omega_f^2 - \omega_f\omega_s - 3\omega_s^2) - 8\omega_b^3(3\omega_f + 3\omega_f\omega_s + \omega_s^2) \right], \quad (B4)
\]

\[
\xi_4 = \frac{4\omega_b\omega_s}{(2\omega_b + \omega_f)^2(\omega_f + \omega_s)^3(2\omega_b + \omega_f + \omega_s)^4} \left[ -3\omega_f^2(2\omega_b + \omega_f)^5 - 3\omega_f^2(2\omega_b + \omega_f)^5 \omega_s + \omega_f^4(2\omega_b + \omega_f)^3 \right.
\]

\[
\left. + \omega_f(2\omega_b + \omega_f)^3(16\omega_b\omega_f - 4\omega_f^2 + 51\omega_f^2)\omega_s^2 + \omega_f(2\omega_b + \omega_f)^2(40\omega_b^2 + 246\omega_b\omega_f + 195\omega_f^2)\omega_s^3 + (2\omega_b + \omega_f)(24\omega_b^3 + 348\omega_b^2\omega_f + 716\omega_b\omega_f^2 + 315\omega_f^3)\omega_s^4 + (160\omega_b^5 + 840\omega_b^4\omega_f + 922\omega_b^3\omega_f^2 + 267\omega_f^5)\omega_s^5 + (160\omega_b^7 + 330\omega_b^6\omega_f + 117\omega_f^7)\omega_s^6 + (50\omega_b + 21\omega_f)\omega_s^7 \right], \quad (B5)
\]

\[
\xi_5 = \frac{4\omega_b\omega_s}{(2\omega_b + \omega_f)^2(\omega_f + \omega_s)^4(2\omega_b + \omega_f + \omega_s)^4} \left[ -3\omega_f^2(2\omega_b + \omega_f)^6 + 3\omega_f^2(\omega_f - 2\omega_b)(2\omega_b + \omega_f)^5 \right.
\]

\[
\left. + 2\omega_f^2(2\omega_b + \omega_f)^4(31\omega_b\omega_f - 2\omega_f^2 + 71\omega_f^2)\omega_s^2 + 2\omega_f^2(2\omega_b + \omega_f)^3(76\omega_b^2 + 404\omega_b\omega_f + 329\omega_f^2)\omega_s^3 + 12\omega_f(2\omega_b + \omega_f)^3(12\omega_b^3 + 135\omega_b^2\omega_f + 271\omega_b\omega_f^2 + 126\omega_f^3)\omega_s^4 + 2(2\omega_b + \omega_f)(24\omega_b^4 + 732\omega_b^3\omega_f + 3034\omega_b^2\omega_f^2 + 3365\omega_b\omega_f^3 + 1036\omega_f^4)\omega_s^5 + 626\omega_b^5\omega_f^2 + 628\omega_b^4\omega_f^3 + 157\omega_b^3\omega_f^4)\omega_s^6 + (556\omega_b^6 + 1036\omega_b^5\omega_f + 283\omega_b^4\omega_f^2)\omega_s^7 + (130\omega_b + 37\omega_f)\omega_s^8 \right], \quad (B6)
\]
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[1] For english translation of the original Michaelis-Menten paper (which was written in german), see (a) R.S. Goody and K.A. Johnson, Biochemistry 50, 8264 (2011), and (b) T.R.C. Boyde, FEBS Lett. 587, 2712 (2013).
[2] FEBS J. 281, issue 2 (2014), special issue (ed. A. Cornish-Bowden) on Enzyme Catalysis and Allostery.
[3] FEBS Lett. 587, issue 17 (2014), special issue (ed. A. Cornish-Bowden and C.P. Whitman) on the centennial of Michaelis-Menten kinetics.
[4] G.E. Briggs and J.B.S. Haldane, Biochem. J. 19, 338 (1925).
[5] V.I. Claessen et al. Annu. Rev. Anal. Chem. 3, 319 (2010).
[6] S.X. Xie, Science342, 1457 (2013).
[7] H. Qian and S.C. Kou, Annu. Rev. Stat. Appl. 1, 465 (2014).
[8] D. Chowdhury, Phys. Rep. 529, 1 (2013).
[9] D. Chowdhury, Biophys. J. 104, 2331 (2013).
[10] A. B. Kolomeisky, J. Phys. Condens. Matt. 25, 463101 (2013).
[11] J. R. Moffitt and C. Bustamante, FEBS J. 281, 498 (2014).
[12] D. Chowdhury, FEBS J. 281, 601 (2014).
[13] J.R. Moffitt, Y.R. Chemla and C. Bustamante, Proc. Natl. Acad. Sci. USA107, 15739 (2010).
[14] W. Jung, S. Yang and J. Sung, J. Phys. Chem. B 114, 9840 (2010).
[15] S. Chaudhury, J. Cao and N.A. Sinitsyn, J. Phys. Chem. B 117, 503 (2013).
[16] J.R. Moffitt, Y.R. Chemla and C. Bustamante, Methods Enzymol. 475, 221 (2010).
[17] K. Nishinari, et al. Phys. Rev. Lett. 95, 118101 (2005).
[18] P. Greulich, et al. Phys. Rev. E 75, 041905 (2007).
[19] A. Garai and D. Chowdhury, EPL, 93, 58004-p6 (2011).
[20] J. Wu and J. Cao, Adv. Chem. Phys. 146, 329 (2012).