Significance of thermal fluctuations and hydrodynamic interactions in receptor-ligand mediated adhesive dynamics of a spherical particle in wall bound shear flow

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Abstract

The dynamics of adhesion of a spherical micro-particle to a ligand-coated wall, in shear flow, is studied using a Langevin equation that accounts for thermal fluctuations, hydrodynamic interactions and adhesive interactions. Contrary to the conventional assumption that thermal fluctuations play a negligible role at high Péclet numbers, we find that for particles with low surface densities of receptors, rotational diffusion caused by fluctuations about the flow and gradient directions aids in bond formation, leading to significantly greater adhesion on average, compared to simulations where thermal fluctuations are completely ignored. The role of wall hydrodynamic interactions on the steady state motion of a particle, when the particle is close to the wall, has also been explored. At high Péclet numbers, the shear induced force that arises due to the stresslet part of the Stokes dipole, plays a dominant role, reducing the particle velocity significantly, and affecting the states of motion of the particle. The coupling between the translational and rotational degrees of freedom of the particle, brought about by the presence of hydrodynamic interactions, is found to have no influence on the binding dynamics. On the other hand, the drag coefficient, which depends on the distance of the particle from the wall, plays a crucial role at low rates of bond formation. A significant difference in the effect of both the shear force and the position dependent drag force, on the states of motion of the particle, is observed when the Péclet number is small.

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I. INTRODUCTION

Particle-substrate adhesion is ubiquitous in biological systems. In the case of cell-surface adhesion, bonding between surface receptors expressed on the cell and complementary ligands expressed on any membrane or cell surface, allow the cell and the surface to specifically adhere to each other like a lock and a key, causing cell adhesion to be highly specific. Some examples are: binding of white blood cells (leukocytes) to particular tissues by specific receptor interactions with endothelial ligands [Springer, 1994]; enhanced adhesion of infected red blood cells to artery and capillary walls due to surface receptors expressed by the malarial parasite, *Plasmodium falciparum* [Cooke et al., 1994; Roy et al., 2005; Antia et al., 2007]; modulation of adhesive properties of cancer cells leading to metastases from the primary tumor through the circulatory system [Cristofanilli et al., 2004; de Bono et al., 2008]; viral docking to cell surface receptors [Alberts et al., 2002; English and Hammer, 2004] etc. *In vitro* experimental techniques such as surface force apparatus, dynamic force spectroscopy, flow chamber experiments and optical trap force spectroscopy have been used extensively to probe various steps in microparticle adhesion.

Modeling and computer simulations further allow one to explore adhesion of particles coated with receptors moving near a ligand-coated substrate under the action of external forces [English and Hammer, 2004; Hammer and Apte, 1992; Korn and Schwarz, 2007, 2008]. Such simulations are now being increasingly used to extract parameters such as rate constants in binding kinetics, binding energies and force constants etc. by fitting model predictions through experimental data [Cristofanilli et al., 2004]. Currently, such studies use the extracted parameters for qualitatively comparing the behaviour of particles with different binding properties *e.g.* healthy and malaria-infected red-blood cells have different adhesins expressed on their surface. The wide interest in drug delivery however suggests that quantitative accuracy may also be desirable for designing particles with specific adhesion targets. There are significant differences however between simulation approaches used in studies so far, particularly in relation to the treatment of thermal fluctuations and hydrodynamic interactions (HI) with the rigid ligand-coated substrate (the “wall”). Our aim is to better understand the role played by these phenomena in determining the states of motion and the dynamics of an adhesive microparticle in a shear flow cell, so that a more judicious choice of simplifying assumptions and simulation approaches can be made depending on
one's end goals.

The Péclet number \( \text{Pe} \) estimates the relative importance of the kinematics enforced by the imposed flow over the Brownian motion caused by thermal fluctuations. Typical shear rates at which shear-cell studies are carried out are around 1-100 s\(^{-1}\). Such shear gradients correspond to very large \( \text{Pe} \) values for microparticles such as cells of size 1–100 µm in an aqueous medium. Typically a high value of \( \text{Pe} \gg 1 \) is assumed to indicate that thermal fluctuations are unimportant, and early simulations of particle adhesion (Hammer and Apte, 1992) ignored thermal fluctuations completely for this reason. They demonstrated that the coupling of the shear flow with the on- and off-kinetics of the receptor-ligand interactions led to various states of motion of an adhesive particle at a wall, such as rolling, firm-adhesion, free diffusion, etc. Korn and Schwarz (2007, 2008) studied these states of motion at high \( \text{Pe} \) values by including Brownian fluctuations. They argued that although thermal fluctuations under such conditions are unimportant for the motion of the particle in the plane of the shear flow, they affect the orientational diffusion of the particle about the gradient direction, bringing receptors into proximity with ligands. This raises two questions: firstly, what if any are the changes to the states of motion when thermal fluctuations are included in high-Pe simulations, and secondly, under what conditions are fluctuations unimportant and hence may be safely neglected in order to design less computationally-intensive simulations (i.e., relatively fast deterministic algorithms).

The adhesion models in the studies cited above incorporate hydrodynamic interactions of the spherical particle with the wall (Hammer and Apte, 1992; Korn and Schwarz, 2007, 2008; Cichocki and Jones, 1998). On the other hand, the Brownian Adhesive Dynamics (BRAD) algorithm of English and Hammer (2004) ignores HI completely to achieve a simpler set of Langevin equations. Wall HI has three principal effects. It causes the friction coefficient to diverge strongly as the wall is approached. Secondly, it leads to significant coupling between the translational and rotational degrees of freedom. These two effects give rise to a position dependent mobility matrix for the particle motion. In addition, the stress distribution on the particle surface induces a net hydrodynamic dipole which causes a flow-induced shear-rate dependent force. The hydrodynamic simplicity of the BRAD algorithm allows for a greater focus on modeling of receptor-ligand interactions, but it is not clear if the net result of HI on dynamical states in a shear flow can be modeled by a simple renormalization of the friction coefficient. This may in turn lead to significant errors when model predictions are used to
interpret experimental observations or to extract interaction parameters.

The following section presents the model used in this study, which is largely based on the one proposed by Korn and Schwarz (2007, 2008). This is followed by a description of the simulation algorithm. Section IV presents a comparison of predictions for high values of Pe obtained in simulations with and without thermal fluctuations, demonstrating that fluctuations are important for low receptor densities even at very large Pe. A simple model is proposed to explain changes in the state diagram. The effect of HI is then explored by systematically turning off different contributions to HI, with our results suggesting that the choice of simpler descriptions of HI in adhesive dynamics simulations depends on the value of Pe.

II. THE MODEL

We simulate the dynamics of spherical particles in a horizontal shear cell with the bottom wall coated by ligands that specifically bind to receptors on the particle surface (Fig. 1). A microparticle is modeled as a rigid sphere of radius $R$. Receptors are modeled as $N_r$, localised reactive patches randomly distributed on the sphere surface each with a spherical capture range of radius $r_0$. Ligands are stationary points on the planar wall distributed on a square grid with spacing $d$ in each direction.

Let $\mathbf{X} = [x, y, z, \theta_x, \theta_y, \theta_z]^T$ denote the six-dimensional state vector in which the first three components are the Cartesian coordinates of the center of the sphere with respect to a fixed frame of reference, and the latter three describe rotation that maps sphere centred coordinate system and the orientation of the sphere to the laboratory fixed coordinate system.

The motion of the particle suspended in a fluid in shear flow near a wall is governed by the following set of coupled Itô stochastic differential equations (SDEs) that account for the translational and rotational Brownian motion of the particle (Korn and Schwarz (2007, 2008)):

$$d \mathbf{X} = \left[ \mathbf{U}^\infty + \mathbf{M} \cdot (\mathbf{F}^D + \mathbf{F}^S) + k_B T \mathbf{M} \cdot \mathbf{M} \right] dt + \sqrt{2k_B T} \mathbf{B} \cdot d \mathbf{W}_t. \quad (1)$$

Here, $k_B$ is the Boltzmann constant, and $T$ is the absolute temperature, and $\mathbf{U}^\infty = \left[ \dot{\gamma} z \ 0 \ 0 \ 0 \ \dot{\gamma}/2 \ 0 \right]^T$ is a 6-dimensional vector containing the translational and rotational unperturbed fluid velocity at the centre of the particle in the absence of the sphere.
Wall HI affects the system through the grand mobility tensor $\mathbf{M}$, and the shear-induced force $\mathbf{F}^S$:

$$\mathbf{F}^S = \begin{bmatrix}
\mathbf{\zeta}^{td} : \mathbf{E}^\infty \\
\mathbf{\zeta}^{rd} : \mathbf{E}^\infty
\end{bmatrix}$$

(2)

where $\mathbf{\zeta}^{td}$ and $\mathbf{\zeta}^{rd}$ are third-rank tensors accounting for the dipolar contributions to translational and rotational friction, respectively, and

$$\mathbf{E}^\infty = \begin{bmatrix}
0 & 0 & \dot{\gamma} \\
0 & 0 & 0 \\
\dot{\gamma} & 0 & 0
\end{bmatrix},$$

(3)

is the rate-of-strain tensor for a homogeneous shear flow of strain-rate $\dot{\gamma}$. Thermal fluctuations are accounted for by $\mathbf{W}_t$, which represents a 6-dimensional Wiener process (Gardiner, 2003; Ottinger, 1996). The tensor $\mathbf{B}$ is chosen such that the fluctuation-dissipation theorem is satisfied and $\mathbf{B} \cdot \mathbf{B}^T = \mathbf{M}$. The positional dependence of the mobility tensor leads to the
additional drift term proportional to $\nabla \cdot \mathbf{M}$ which is necessary to ensure that the governing Itô SDEs (Eq. 1) are consistent with a Fokker-Planck equation for the probability density of the particle position and orientation (Gardiner, 2003; Öttinger, 1996). The tensors $\mathbf{M}$, $\mathbf{\zeta}^{td}$ and $\mathbf{\zeta}^{rd}$ and $\mathbf{B}$ depend on the distance of the particle centre from the wall $z$ and its radius $R$; details of the calculation of these tensors and $\nabla \cdot \mathbf{M}$ have been summarized by Korn and Schwarz (2007).

The vector $\mathbf{F}^D$ denotes the sum of all direct conservative forces and resulting torques acting on the sphere. The first contribution to this generalized force vector comes from a constant attractive force $\mathbf{F}^G = [00F^G000]^T$ towards the wall. The primary role of this force in our simulations is to ensure a steady-state distribution for the particle to be at height $z$ to have a peak at the wall. The second contribution to $\mathbf{F}^D$ comes from the weak non-covalent bonds formed between receptors and ligands. Each receptor-ligand bond is modeled as a semi-harmonic spring, and its contribution to the total force $\mathbf{F}^D$ depends on the instantaneous bond length $r_b$ between centres of the receptor and ligand involved in the bond:

$$
\mathbf{F}_b = \begin{cases} 
\kappa (r_b - \ell_0) \hat{r}_b, & \text{if } r_b > \ell_0, \\
0, & \text{otherwise.}
\end{cases}
$$

where $\kappa$ is the spring stiffness, $\ell_0$ is the rest length of a bond, and $\hat{r}_b$ is the unit vector from the receptor centre on the sphere surface to the ligand on the wall. The torque exerted by this force on the sphere is evaluated as $\mathbf{T}_b = \bar{r} \times \mathbf{F}_b$, where $\bar{r}$ is the position vector of that receptor on the sphere surface relative to the sphere centre.

Ligands are placed on the wall as a periodic square lattice with spacing $d$; in other words, the ligand density on the wall scales as $1/d^2$. Receptors are distributed randomly on the sphere surface while ensuring that no two receptors overlap within a radius of $r_0$. The receptor density is $N_r/(4\pi R^2)$, where $N_r$ is the total number of receptors on the sphere surface. A receptor-ligand bond can form when a pair is within a distance of $r_0$ from each other. Bonds are established at a mean rate of $k_{on}$, whereas each bond dissociates at a mean rate given by Bell’s equation (Bell, 1978):

$$
k_{off} = k_{off}^0 \exp\left(\frac{F_b}{F_c}\right),
$$
where $k_{\text{off}}^0$ is the unstressed bond dissociation rate, and $F_c$ is a reactive compliance force scale. Eq. (3) indicates an exponential increase in the dissociation rate with the bond force.

The dimensional model parameters include the viscosity of the ambient fluid $\eta$, its absolute temperature $T$, the particle radius $R$ and the shear-rate $\dot{\gamma}$. To express equations and parameters in dimensionless form, we choose $R$, $1/\dot{\gamma}$ and $6\pi\eta R^2/\dot{\gamma}$ as the characteristic length, time and force scales in the problem. The key dimensionless parameters whose effect we study in our simulations are the Péclet number, $\text{Pe} = 6\pi\eta R^3/\dot{\gamma}$, the on-rate $\pi = k_{\text{on}}/\dot{\gamma}$, the off-rate $\varepsilon_0 = k_{\text{off}}^0/\dot{\gamma}$, and the receptor density, $N_r$. Unless otherwise specified, all parameters and variables henceforth will be dimensionless, having been rescaled by the scales given above. We keep all other parameters fixed at values typical of shear-cell experiments with leukocytes suspended in water at room temperature (Korn and Schwarz, 2008): $\text{Pe} = 425 — 42566; \pi = 10^{-3} — 50; \varepsilon_0 = 10^{-4} — 10^3; N_r = 10 — 5 \times 10^3$; gravitational force, $F_G = 5 \times 10^{-3}$; receptor size and capture radius, $r_0 = 10^{-2}$; ligand spacing, $d = 5 \times 10^{-2}$; reactive compliance $F_c = 5.3$; bond stiffness, $\kappa = 118$; the bond rest length is the receptor-ligand distance at the instance of bond formation. These are obtained by using $R = 4.5 \mu m$ and $\dot{\gamma} = 100$ s$^{-1}$ and $\eta = 10^{-3}$ Pa s, relevant to leukocytes in an aqueous medium. Ligand density is $1/d^2 = 400$ and the receptor density with $N_r = 10$, and $N_r = 5000$, is 0.796 and 398, respectively.

Our primary observables that help determine the state of motion of a particle near the wall are the average translational velocity in the flow direction $\langle U_x \rangle$ and the average rotational velocity in the flow plane $\langle \Omega_y \rangle$, and their respective variances $\sigma_U$ and $\sigma_\Omega$. Based on their values it is possible to identify distinct states of motion (Korn and Schwarz, 2008). If no bonds are formed, the particle achieves a steady-state average velocity, which we refer to as the hydrodynamic velocity $\langle U_x \rangle_{\text{hd}}$. This is the maximum average velocity a particle can attain. When bond formation is insignificant, $\langle U_x \rangle$ with the adhesion kinetics is nearly equal to $\langle U_x \rangle_{\text{hd}}$, and the particle is stated to be in a state of “free-motion”. If bond-formation and disassociation are both significant, the particle can roll at the wall with $\langle \Omega_y \rangle/\langle U_x \rangle \approx 1$. When $\text{Pe} \gg 1$, and if bond formation dominates over disassociation, the particle is nearly always firmly adhered with the surface, and $\langle U_x \rangle \approx 0$. If bond breakage is a little higher, it is possible to obtain stick-slip motion which is referred to as “transient adhesion” by Korn and Schwarz (2008). Table II summarizes the criteria they suggest for distinguishing between these states. It must be noted that the instantaneous velocities in a stochastic
trajectory are not well-defined quantities. The way the averages are calculated is explained in the next section (III).

TABLE I. Criteria for determining states of particle motion (Korn and Schwarz, 2008)

| State                        | Definition                                                                 |
|------------------------------|---------------------------------------------------------------------------|
| Free motion                  | $\langle U_x \rangle > 0.95 \langle U_x \rangle_{hd}$                    |
| Rolling adhesion             | $\langle \Omega_y \rangle / \langle U_x \rangle > 0.8$ and $0.95 > \langle U_x \rangle / \langle U_x \rangle_{hd} > 0.01$ |
| Firm adhesion (FA)           | $\langle U_x \rangle < 0.01 \langle U_x \rangle_{hd}$                    |
| Transient adhesion I (TA I)  | $\langle U_x \rangle / \langle U_x \rangle_{hd} > 0.01$ and $\langle \Omega_y \rangle / \langle U_x \rangle < 0.8$ and $\sigma_U / \langle U_x \rangle < 0.5$ |
| Transient adhesion II (TA II)| $\langle U_x \rangle / \langle U_x \rangle_{hd} > 0.01$ and $\langle \Omega_y \rangle / \langle U_x \rangle < 0.8$ and $\sigma_U / \langle U_x \rangle > 0.5$ |

III. SIMULATION ALGORITHM

The coupled set of SDEs in Eq. (1) are integrated numerically using an Euler discretization (Ottinger, 1996). The discrete equation is:

$$\Delta X_t = \left[ U^\infty + M \cdot (F^D + F^S) + \frac{1}{Pe} \nabla \cdot M \right] \Delta t + \sqrt{\frac{1}{Pe} B} \cdot \Delta W_t. \quad (6)$$

The Wiener increment $\Delta W_t$ in the equation above is a vector with 6 components, each of which is a Gaussian random number with zero mean and variance $2\Delta t$. The well-known Box-Muller algorithm is first used to transform uniformly distributed random numbers in the interval $(0, 1)$ to Gaussian random numbers, which are then multiplied by $\sqrt{2\Delta t}$ to generate the Wiener increment.

The time-step size $\Delta t$ is chosen to be smaller than all the relevant physical time scales of the system, which are the following: the dimensionless diffusive time scale over which the sphere diffuses in bulk fluid over a distance equal to its own radius is $Pe$. However, when the sphere is close to the wall and adhesion kinetics are important, the time scale over which the sphere diffuses through a length scale corresponding to the size of a receptor is estimated as $\tau_r = Pe (r_0/R)^2$. The dimensionless time-scale corresponding to the bond stiffness is $\tau_f = \kappa^{-1}$. The time scales associated with the on and off-rates are $1/\pi$ and $1/\epsilon_0$ respectively.
A single simulation for a given set of parameters consists of an ensemble of stochastic particle trajectories. In each trajectory, the initial position of the sphere centre is set as \((x, y, z) = (0, 0, 1 + r_0)\). Receptor locations are distributed on the sphere surface by randomly (i.e. according to a uniform distribution) choosing a set of \(N_r\) azimuthal and polar angles in the intervals \([0, \pi]\) and \([0, 2\pi]\), respectively. If the distance between a receptor and any of the previously chosen receptors is less than \(r_0\), the choice is rejected, and a new location is chosen. Once all receptors are located, two separate tables storing the positions of each receptor are created. One stores the coordinates of the position vectors of each receptor in the laboratory-fixed co-ordinate system. The other stores the position vectors \(\mathbf{n}_i\) of each receptor \(i\) in a co-ordinate system fixed to the center of the sphere and oriented parallel to the laboratory-fixed co-ordinate system.

A single time-step in the simulation involved the following sequence of calculations.

1. Using the position of the centre of the particle, the mobility tensor \(\mathbf{M}\) and related quantities \(\mathbf{F}^S\), \(\nabla \cdot \mathbf{M}\) and \(\mathbf{B}\) are calculated using the method described by Korn and Schwarz (2007). This requires the evaluation of several scalar functions of \(z\) which are calculated before the start of the simulation and stored in a discrete look-up table. Values at any required \(z\) are obtained at each time-step by interpolating between entries in the look-up table.

2. A table of receptors in the contact zone is updated. All receptors for which the arc-length from the lower apex of the sphere is less than \(\delta = 2r_0\), are included in the list. Another list of ligands in the contact zone is updated, where the position of these ligands is calculated from the co-ordinates of the sphere centre.

3. The table of bonded receptors and ligands is updated with new bonds. This involves giving every unbonded receptor-ligand pair in the contact zone a chance to form a bond. If the distance between an unbonded pair is less than \(r_0\), the probability that a bond is formed follows Poisson statistics, and is \(p_{\text{on}} = 1 - \exp(-\pi \Delta t)\) (\(\pi\) here is the dimensionless on-rate). Following a Metropolis scheme, a uniform random number is chosen in \([0, 1]\); if it is less than \(p_{\text{on}}\), the receptor and ligand are assigned as bonded, and removed from the unbonded list of pairs.

4. The list of bonded pairs is then scanned to calculate all the bond forces (Eq. (4)) and
their moments about the particle centre.

5. Each bond is then given a chance to dissociate with a probability \( p_{\text{off}} = 1 - \exp(-k_{\text{off}} \Delta t) \), where the bond-force dependent \( k_{\text{off}} \) is calculated for each bond according to Eq. (5). Bond dissociation is also implemented following a Metropolis scheme. All dissociated receptors and ligands are removed from the bond table, and their bond forces and torques are set to zero.

6. The total bond force and torque are calculated, and this is added to the gravitational force to obtain the non-hydrodynamic force vector \( \mathbf{F}_D \) in Eq. (7).

7. The displacement vector \( \Delta \mathbf{X}_t \) is calculated according to Eqn. (6), and the position and orientation of the sphere is updated. Wall penetration is prevented by a bounce-back criterion: if \( z(t + \Delta t) < 1 \) after the update, it is reassigned as \( z(t + \Delta t) = z(t) + |\Delta z| \).

8. The receptor location table containing \( \mathbf{n}_i \) is updated using the Rodrigues formula:

\[
\mathbf{n}_i(t + \Delta t) = \mathbf{n}_i(t) \cos \theta + (\hat{\theta} \times \mathbf{n}_i) \sin \theta + \hat{\theta} (\hat{\theta} \cdot \mathbf{n}_i) (1 - \cos \theta)
\]

where \( \theta = (\Delta X_4, \Delta X_5, \Delta X_6) \), \( \theta = |\theta| \), and \( \hat{\theta} = \theta / |\theta| \). Following this, the receptor locations in the laboratory-fixed frame is updated by adding the sphere centre position vector to each \( \mathbf{n}_i \).

Each trajectory is allowed to equilibrate for a long time before sampling particle position and orientation co-ordinates and the number of extant bonds at regular intervals. The length of the equilibration time required to achieve a stationary distribution varies with bond kinetic parameters. As will be shown later, an estimate of this time-scale can be derived. Using these estimates and other standard tests, we ensure that true steady states are obtained. The values of \( \langle U_x \rangle \) and \( \langle \Omega_y \rangle \) and their variances are calculated from net displacements between sampling intervals. Averages at each sampling time are calculated as ensemble averages over a large number of independent trajectories. For each Pe value, the hydrodynamic velocity \( \langle U_x \rangle_{hd} \) is determined in a simulation with all bond interactions turned off.
IV. RESULTS AND DISCUSSION

Keeping all the parameters fixed and varying the bond on and off rates $\pi$, and $\varepsilon_0$, the average velocities and their variances are calculated and a state diagram is obtained. Figure 2 shows the state diagram with five stationary states as defined in table 1. The parameters used are listed in the figure caption. With the parameter values chosen, the Péclet number turns out to be 42566. The figure, which is identical to the published data of Korn and Schwarz (2008), serves as a validation of our simulations.

IV.1. Significance of thermal fluctuations

To demonstrate the significance of thermal fluctuations, we neglect the Gaussian noise contribution in Eq. (6) in order to switch-off Brownian fluctuations.

At high Péclet number, $\text{Pe} = 42566$, no significant differences were found between the state diagrams with and without thermal fluctuations, as can be seen from Fig. 3. The translational and angular velocities that determine the dynamics of the sphere were also
found to be similar, showing no distinction between the two cases. This suggests that the role of thermal fluctuations on the dynamics of receptor-ligand mediated micro-particle adhesion for high Pe is not significant. This is in line with our intuition, since Pe is equal to the ratio of convective to the thermal forces. It is to be noted that the simulations were conducted for high receptor numbers, \( N_r = 5000 \).

When the number of receptors was reduced to \( N_r = 100 \) and \( N_r = 10 \), from \( N_r = 5000 \) (with all the other parameters kept the same), and simulations were carried out with fluctuations, three significant differences were observed: (1) there is disappearance of the rolling region, (2) there is an expansion of the transient II region such that the rolling regime present for \( N_r = 5000 \) is modified to transient motion for \( N_r = 100 \) and \( N_r = 10 \), and, (3) there is a shift of all the states from the upper left region of the state diagram for the \( N_r = 5000 \) case towards the lower right region. However, as in the case for \( N_r = 5000 \), the state diagram at \( N_r = 100 \) does not show any significant effect of thermal fluctuations.

The state diagrams with and without fluctuations for \( N_r = 10 \) are displayed in Fig. 4. The states of motion with fluctuations in Fig. 4 (a) are distinguished by filled areas, and the results of simulations without fluctuations are presented as boundaries with continuous lines. For the sake of clarity the same boundaries without fluctuations in Fig. 4 (a) are shown.
FIG. 4. On-off state diagram with and without thermal fluctuations at $N_r = 10$ (all other parameter values are as given in Fig. 2). (a) Filled regions represent the states of motion with thermal fluctuations and lines are boundaries between states of motion without thermal fluctuations. Firm adhesion is not seen without fluctuations. (b) Explicit display of the state diagram without fluctuations (using filled regions) to highlight the absence of the firm adhesion regime. Bond averages and average velocities along the vertical dashed line at $\pi=10$, are shown in Figs. 5 and 6 respectively. The following observations can be made: (1) absence of a firm adhesion region when thermal fluctuations are absent, and (2) significant difference in the boundaries (of free motion and) transient regions at lower on-rates. For the firm adhesion state to exist, the average number of bonds must be greater than 1 such that a cell (particle) is completely arrested. In Fig. 4(a), in the parameter range of $(\pi, \varepsilon_0)$, corresponding to the
FIG. 5. Average number of bonds for $N_r=10$, at $\pi=10$, with and without thermal fluctuations. Subscript B denotes the case with Brownian fluctuations, and D denotes without fluctuations. Clearly $\langle n_b \rangle$ without thermal fluctuations never reaches 1, indicating the absence of the firm adhesion region.

firm adhesion region in the presence of fluctuations, the average number of bonds is 0.96 – 1.4. This is reduced to 0.34 – 0.48 when thermal fluctuations are ignored. Fig. 5 shows the variation of the average number of bonds, at $\pi=10$ (indicated by the vertical dashed line in the state diagrams, Figs. 4), with the bond off-rate $\varepsilon_0$. The bond number never reaches one in the absence of thermal fluctuations, indicating disappearance of the firm adhesion region. This suggests that the rotational diffusion of the particle enables (facilitates) the receptors to be available for bond formation when the receptor density is very low.

Figure 6 shows that the translational as well as angular velocities are considerably reduced, (to almost zero) at low values of $\varepsilon_0$ (for a fixed vale of $\pi$) in the presence of thermal fluctuations, unlike for the case without. The expansion of the transient region in Fig. 4 (a) can be attributed to a fewer number of bonds controlling the dynamics (Fig. 5). When a single bond is at work, depending upon the off-rate, it can either capture the particle or decelerate it, and the transient II or transient I states are respectively seen. For rolling to occur, whatever the current state of motion is, it should be supported by subsequent formation of bonds. This can happen when there are at least two bonds possible on an average. Figure 5 shows that the average bond number never reaches 2 for both the cases of with and without fluctuations. This explains the absence of rolling in the state diagram for $N_r=10,$
FIG. 6. Translational and angular velocities with and without thermal fluctuations at $N_r=10$ and $\pi=10$. Subscript B denote the case with Brownian fluctuations and with D denote without fluctuations. Without fluctuations, the velocities do not reach zero and therefore no firm adhesion region exists.

FIG. 7. Schematic diagram showing a sphere distributed with receptors of radius $r_0$, with the plane of the seam parallel to the $y$-axis.

Unlike that seen for $N_r=5000$.

A better understanding of the role of thermal fluctuations at low $N_r$ can be obtained with the help of a simple analytical model. Basically, an estimate of the ratio of the steady-state average number of bonds with and without fluctuations can be derived, for a sphere with
just a single receptor, and a high density of ligands on the wall, as shown in the schematic diagram in Fig. 7.

Consider the case of a single receptor on a sphere of radius $R$, as in Fig. 7. The mean time for first bond formation, when the sphere spins along the $y$-axis with an angular speed of $\omega$, parallel to the wall, can first be estimated in the absence of thermal fluctuations. A bond in this case can form only if the receptor lies in the seam region of width $r_0$ and area $2\pi r_0 R$. The radius of the receptor is the width of the seam. When the plane of the seam is perpendicular to $y$-axis and if any receptor lies on this seam then there is a probability of forming a bond with the ligand. The mean bond number over the entire ensemble, including initial orientations of favourably and unfavourably placed receptors is

$$\langle n_b \rangle_{\text{no fluc.}} = P_{\text{seam}} \overline{n}_b$$

where, $P_{\text{seam}} = (r_0/2R)$ is the probability that a receptor lies in the seam initially, and $\overline{n}_b$ is the time averaged number of bonds on any single favourable trajectory, given by

$$\overline{n}_b = \frac{\overline{\tau}_{\text{bonded|seam}}}{\overline{\tau}_{\text{unbonded|seam}} + \overline{\tau}_{\text{bonded|seam}}}$$

where, $\overline{\tau}$ is the mean time that the receptor is bonded or unbonded. Detailed derivation of the expressions for $\overline{\tau}$ when bonded and unbonded are given in Appendix A. Hence,

$$\langle n_b \rangle_{\text{no fluc.}} = \left( \frac{r_0}{2R} \right) \left( 1 - e^{-k_{\text{on}}r_0/(R\omega)} \right) \left( \frac{1 - e^{-k_{\text{off}}/(R\omega)}}{2\pi k_{\text{off}}/\omega + 1 - e^{-k_{\text{on}}r_0/(R\omega)}} \right).$$

(9)

If thermal fluctuations are switched on, there are two important differences. Firstly, the ensemble of trajectories is no longer segregated into ones with favourable or unfavourable initial conditions; all trajectories are statistically equivalent. Secondly, over any single long trajectory, we can distinguish times in which the receptor is bonded, times when it is on the seam and unbonded and times when it is outside the seam and unbonded. In this case,

$$\langle n_b \rangle_{\text{fluc.}} = \frac{\overline{\tau}_{\text{bonded|seam}}}{\overline{\tau}_{\text{seam + nonseam}}}$$

(10)

Therefore,

$$\langle n_b \rangle_{\text{fluc.}} = \left( \frac{r_0}{2R} \right) \left( 1 - e^{-k_{\text{on}}r_0/(R\omega)} \right) \left( \frac{1 - e^{-k_{\text{off}}/(R\omega)}}{(2R/r_0)(2\pi k_{\text{off}}/\omega) + 1 - e^{-k_{\text{on}}r_0/(R\omega)}} \right).$$

(11)
Finally the ratio,

\[
\frac{\langle n_b \rangle_{\text{fluc.}}}{\langle n_b \rangle_{\text{no fluc.}}} = \frac{2\pi k_{\text{off}}/\omega + 1 - e^{-k_{\text{on}}r_0/(R\omega)}}{2\pi k_{\text{off}}/\omega + (1 - e^{-k_{\text{on}}r_0/(R\omega)}) (r_0/2R)}
\]  

(12)

For fixed \( k_{\text{on}} \), when \( k_{\text{off}} \) is large, the mean number of bonds is low, indicating free motion. As \( k_{\text{off}} \) is decreased the bond average, \( \langle n_b \rangle_{\text{fluc.}} \to 1 \), and \( \langle n_b \rangle_{\text{no fluc.}} \to r_0/(2R) \). Therefore for a single receptor, as off-rate is decreased, a transition from free-motion to firm adhesion should be seen. However, in the absence of thermal fluctuations, firm adhesion is never observed, since \( r_0 \ll R \). Thus, fluctuations are essential for binding at low number of receptors. Figure 5 corroborates the above arguments and shows that at lower off-rates \( (\varepsilon_0 = k_{\text{off}}^0/\dot{\gamma}) \). \( \langle n_b \rangle \) approaches 1 in the presence of fluctuations, confirming the firm adhesion regime seen in Fig. 4 (a). In the absence of fluctuations, as seen in Fig. 5, \( \langle n_b \rangle < 1 \), which is in qualitative agreement with Eq. (9), indicating the absence of a firm adhesion region, as seen in the on-off state diagram, Fig. 4 (b).

IV.2. Significance of hydrodynamic interactions

The dynamics of a spherical particle near a wall in shear flow can be strongly affected by the position of the particle relative to the wall, since hydrodynamic interactions of the particle with the wall is strongly position dependent. Hydrodynamic interactions enter the structure of the governing equations in three ways. Firstly, the drag coefficient, represented by the diagonal part of the mobility matrix \( \mathbf{M} \), sensitively depends upon the height of the particle \( z \) from the wall (Fig. 1). Secondly, HI leads to a coupling between translational and rotational degrees of freedom through the non-diagonal terms of \( \mathbf{M} \). Finally, in addition to the position dependent mobility tensor, a third contribution arises from the shear-induced force \( \mathbf{F}^S \). To investigate the role of wall HI on adhesive dynamics, we study each of these effects of HI by selectively switching off appropriate terms in the simulations, while keeping thermal fluctuations intact. Note that for simulations with absolutely no HI, the mobility matrix is position independent, specifically, the diagonal terms are \( 1/(6\pi \eta R) \) and \( 1/(8\pi \eta R^3) \), which correspond to the force and the torque, respectively. The off-diagonal terms are all zero, and \( \mathbf{F}^S \) is also zero. Apart from “full HI” and “no HI”, we define “partial HI”, with \( z \) dependent diagonal terms, as having two flavours: The first is with \( \mathbf{F}^S = 0 \), but with all
other terms in Eq. (6) present (denoted here as “no shear HI”), and the second, with the off-diagonal elements of $M$ also set equal to zero (in addition to $F_S = 0$), which we denote here as “no shear-no coupling HI”.

Figure 8 shows the state diagram of particle adhesion in the $\pi - \varepsilon_0$ space with these three forms of HI for the case of $N_r = 5000$ at $Pe = 42566$. For “full HI” the states of motion are distinguished by areas filled with different colours. For “no HI” and “partial HI” only the boundaries between the states are shown. Since we found complete overlap of boundaries for the two forms of “partial HI”, they are both represented by dotted lines in Fig. 8. This indicates that there is no effect due to the coupling of the translational and rotational degrees of freedom, on the steady state motion of the particle. This is further illustrated in Figs. 9 which shows that the translational and angular velocities for “no shear-no coupling”, and “no shear HI” are nearly the same at both $\pi = 0.15$, and $\pi = 10$. For these reasons, from here onwards in the paper, the phrase “partial HI” will be used to mean the case of “no shear-no coupling HI”.

When the off-rate is reduced from a high to a low value at a constant on-rate, the particle undergoes a transition from free motion to firm adhesion via TA-I, TA-II and rolling regimes. It can be seen from Fig. 8 that although wall HI has little effect on the free motion regime,
it plays a significant role in the transitions between other states of motion, where important differences are observed at lower and higher on-rates \( \pi \). At lower on-rates, \( 0.01 \leq \pi \leq 0.2 \), the “partial HI” and “no HI” cases show an upward displacement of the boundaries as compared to the “full HI” case, with the shift being more significant in the case of “no HI” as compared to “partial HI”. More over, the “no HI” case results in a disappearance of the transient-I region. At higher on-rates \( (\pi \geq 0.3) \), however, the “no HI” and “partial HI” boundaries nearly coincide and show an upward shift at the firm adhesion–rolling cross over as well as rolling–transient cross over boundaries with respect to the “full HI” boundaries. This manifests as a higher off-rate \( \varepsilon_0 \) for firm adhesion and rolling to set in. It is to be noted that the state diagram is not a mere translational shift of the boundaries since the free motion boundary remains pinned for the different cases of HI considered here.

A careful analysis provides the reasons for the observations drawn from Fig. 8. When a bond is formed it pulls the sphere against the flow with a force \( F_x \) in the \( x \)-direction. The detachment force acting on the sphere with “full HI” is \( 6\pi \eta R \dot{\gamma} z / \varepsilon + F^S_x \), (where \( \varepsilon ( \leq 1) \) is the correction to the drag coefficient due to the presence of wall and \( F^S_x \) is the shear force in flow direction). In the absence of HI, the detachment force is \( 6\pi \eta R \dot{\gamma} z \), which is smaller than the drag force \( (6\pi \eta R \dot{\gamma} z / \varepsilon) \) with “partial HI”. Therefore, a bonded particle experiences a greater drag force when “partial HI” is acting relative to “no HI”. On the other hand, “full HI” has an extra contribution of shear force \( F^S \), leading to an even larger detachment force.

Since the maximum bond force balances the hydrodynamic force at equilibrium, the Bell equation (Eq. 5) indicates that the effective off-rate is high with “partial HI”, and even higher with “full HI”, for the same values of \( k_{\text{off}}^0 \) (and \( \varepsilon_0 \)). Qualitatively, it could be said that the effective off-rate follows the hierarchy, \( \varepsilon_{\text{eff}}^{\text{full}} > \varepsilon_{\text{eff}}^{\text{p-HI}} > \varepsilon_{\text{eff}}^{\text{no-HI}} \). As can be seen in Fig. 8 due to the greater effective off-rate, “full HI” leads to the firm adhesion state being obtained at comparatively lower values of \( \varepsilon_0 \), at all values of on-rates. The relative differences in off-rates also explains the changes seen in the state diagram at lower on-rates, showing a progressive upward shift of the firm adhesion–transient II boundary in the “partial HI” and “no HI” cases, compared to the “full HI” case.

The Bell equation (Eq. 5), in non-dimensional form is \( \varepsilon = \varepsilon_0 \exp(F_b/F_c) \) where \( F_b \) and \( F_c \) are non-dimensional. It has two parts, one is force independent \( \varepsilon_0 (= k_{\text{off}}^0 / \dot{\gamma}) \) and the other is force dependent part. At higher values of \( \varepsilon_0 \) at which free motion boundary occurs, \( \varepsilon_0 \)
dominates in the Bell equation as the shear force and position dependent drag force are not comparitively significant. This results in no perceptible change in the free motion boundary for all the three cases of HI. However at lower $\varepsilon_0$ values, hydrodynamic forces contribution to the force dependent part of Bell equation seems to be significant.

More insight into the role of HI can be obtained from Fig. 9, which compares the effect of HI on the translational and angular velocities at $\pi = 0.15$, and $\pi = 10$. At higher values of $\varepsilon_0$, translational and angular velocities with “no HI” and “partial HI” are seen to be nearly twice the values in the presence of “full HI”, which implies that the shear force $F^S$ reduces the velocity significantly. Further it is observed the velocities approach zero at higher off-rates in the case of the “no HI”, indicating that bond breakage is assisted by HI. Additionally, at

FIG. 9. Average velocities with “full HI”, “partial HI”, “no shear HI” and “no HI” at $\text{Pe}=42566$, $N_r=5000$. (a) Translational velocity at $\pi=10$ (b) Angular velocity at $\pi=10$, (c) Translational velocity at $\pi=0.15$ (d) Angular velocity at $\pi=0.15$. $\pi=10, 0.15$ represent the values at the verticle lines shown in fig.[8].
The BRAD algorithm, which completely ignores HI, has been used for simulating the dynamics of viruses (English and Hammer (2004)). The small size of viruses implies that the Péclet number for such problems is low. It is consequently interesting to explore the influence of HI on the adhesive dynamics of spherical particles at low Péclet numbers. The state diagram at Pe = 425 is shown in Fig. 10 for all the three cases of HI discussed previously for Pe = 42566. At higher values of π, no significant difference is seen in the state diagram between the “no HI”, “partial HI” and the “full HI” cases. Since $\dot{\gamma} \propto Pe$ and $F_S \propto \dot{\gamma}$, the influence of $F_S$, which was seen to be significant for Pe = 42566, diminishes at Pe = 425. The force dependent part of the Bell equation does not seem to matter at these values of π, thereby mitigating the influence of HI. At low values of π, the transient regions for the “partial HI” case become narrower, while they disappear entirely for the “no HI” case.

Figures 11 show the differences in the velocities at π = 10 and π = 0.04. The hydrodynamic velocity $\langle U_x \rangle_{hd}$ (i.e., the velocity of a freely moving particle, which occurs at high values of
π) with “full HI”, is seen to be closer to the hydrodynamic velocities of the “no HI” and “partial HI” cases, where as at Pe = 42566 it was seen to be nearly twice as large. This also indicates that RS is insignificant in the low Pe regime. Figures 11 (a) and (b) show that at π=10, the velocities approach zero at roughly the same value of ε0, and with qualitatively similar motion. This corroborates the independence of the state diagram from HI at high values of π. On the contrary, at low values of π (Figs 11 (c) and (d)) the velocity with “no HI” goes to zero at a higher value of ε0 compared to the “partial HI” and “full HI” cases. This is in qualitative agreement with the state diagram at low values of π, which shows that the firm adhesion–transient boundary is progressively shifted upwards, for reasons similar to those discussed earlier at high Péclet numbers. Notably, the transition from hydrodynamic velocity to zero velocity with decreasing ε0 is gradual in the case of “full HI”, less so with “partial HI”, and rapid when there is no HI. This is reflected in the state diagram (Fig. 10) as changes in the respective transient adhesion regions.

The BRAD algorithm study of virus dynamics by English and Hammer (2004) was carried out in the absence of flow, and consequently, shear forces were absent. However, we have seen that when the bond on-rates are small, the effect of “partial HI” is significant, indicating that the position dependent mobility tensor can affect bond dynamics. Ignoring the position dependent drag will lead to poor estimates of kinetic parameters when they are extracted by a comparison of simulations with experimental data. It seems more appropriate to use Eq. (11), with the mobility tensor containing only the diagonal elements (in their full form, with position dependent mobility functions), to obtain a more accurate understanding of adhesive dynamics at low Péclet numbers. If the system admits flow, then the complete Eq. (11) must be simulated for an accurate exploration of receptor ligand binding kinetics.

V. CONCLUSIONS

At high receptor numbers (Nr > 100), there appears to be no significant effect of thermal fluctuations on the adhesive dynamics of a micro-particle in shear flow near a wall. However, thermal fluctuations are seen to be important at low receptor numbers (Nr = O(10)). For instance, thermal fluctuations enhance the particle’s ability to adhere firmly to the wall, reflected in the observation that at Nr = 10, the firm adhesion regime disappears when thermal fluctuations are ignored. Such effects should “in-principle” be observable in experiments.
with bio-particles, such as cells and viruses, which have relatively few receptors.

The significance of hydrodynamic interactions in obtaining the correct dynamic states of a micro-particle adhering to a wall has also been established. Our simulations indicate that the role of HI is not just a renormalisation of the axes. For instance, at high Péclet numbers, the shear induced force is found to assist in the disassociation of receptor-ligand bonds, leading to significant changes in the state diagram. The free motion of the particle, however, is unaffected by the presence of HI, and the coupling between the translational and

FIG. 11. Comparison of translational and angular velocities with “full HI”, “partial HI” and “no HI” at Pe=425 and Nr=5000 (a) at \( \pi=10 \), (b) at \( \pi=0.04 \).
rotational degrees of freedom of the particle, has no effect on binding dynamics.

At low Péclet numbers, both the shear induced force and the position dependent drag force have no effect on the state diagram when the rates of bond formation are high. On the other hand, both these aspects have a significant effect at low bond formation rates. This suggests that the inclusion of a position dependent friction coefficient in the BRAD algorithm, typically used at low Péclet numbers, is recommended in order to capture adhesive dynamics accurately.

Appendix A: Derivation for the ratio of average bond number with and without thermal fluctuations

Consider the case of a single receptor on a sphere of radius $a$. We want to estimate the mean time for first bond formation, when the sphere spins along the $y$-axis parallel to the wall with an angular speed of $\omega$, and firstly, in the absence of thermal fluctuations. A bond in this case can only form if the receptor lies in the seam region of width $r_0$ and area $2\pi r_0 R$. The probability that a receptor lies in the seam initially is hence $P_{\text{seam}} = 2\pi r_0 R/(4\pi R^2) = r_0/(2R)$. The first-order reaction kinetics for bond-formation essentially implies that bond formation proceeds as a Poisson process with a mean rate $k_{\text{on}}$. Now if a receptor lies in the seam, then its residence time in the reaction zone of size $r_0 \times r_0$ is $\tau_r = r_0/(R\omega)$. Given that the receptor lies on the seam, the conditional probability that adhesion occurs within this residence time, for any single pass of the receptor across the ligand, is 1 minus the probability that no bond forms at all within $\tau_r$. From the statistics for a Poisson process

$$P_{\text{bond|seam}} = 1 - \frac{e^{-k_{\text{on}}\tau_r}(k_{\text{on}}\tau_r)^0}{0!},$$

If this is the probability that a bond forms in one pass, then the mean number of passes before a bond is formed is $1/P_{\text{bond|seam}}$. Since we have one pass per revolution, and the time for one revolution is $2\pi/\omega$, the mean time before first bond formation, or the mean time for
which the receptor is unbonded, given a receptor is on the seam is

\[
\tau_{\text{unbonded}|\text{seam}} = \frac{2\pi}{\omega P_{\text{bond}|\text{seam}}} = \frac{2\pi}{\omega \left(1 - e^{-\kappa_{\text{on}} r_0/(R\omega)}\right)}.
\]

(A2)

Once a bond forms the mean time for it to de-bond, or the mean-time for which the receptor is bonded, is just \(\tau_{\text{bonded}|\text{seam}} = 1/k_{\text{off}}\), since the spin is switched off once a bond forms. Since a bond is present only during the time debonding takes place, the time-averaged number of bonds on any single on-seam-receptor trajectory is hence

\[
\langle n_b \rangle = \frac{\tau_{\text{bonded}|\text{seam}}}{\tau_{\text{unbonded}|\text{seam}} + \tau_{\text{bonded}|\text{seam}}} = \frac{1/k_{\text{off}}}{\frac{2\pi}{\omega \left(1 - e^{-\kappa_{\text{on}} r_0/(R\omega)}\right)} + 1/k_{\text{off}}} = \frac{2\pi k_{\text{off}}/\omega + 1 - e^{-\kappa_{\text{on}} r_0/(R\omega)}}{2\pi k_{\text{off}}/\omega + 1 - e^{-\kappa_{\text{on}} r_0/(R\omega)}}.
\]

(A3)

Note that in order to reach a steady state, we need to sample over a time scale greater than \(\tau_{\text{unbonded}|\text{seam}} + \tau_{\text{bonded}|\text{seam}}\) which diverges as either \(k_{\text{on}}\) or \(k_{\text{off}}\) \(\to 0\). The result above is the average over the trajectories that start with a favourably-placed receptor. The mean bond number over the entire ensemble, including those initial orientations that can never form a bond is

\[
\langle n_b \rangle = P_{\text{seam}} \langle n_b \rangle = \frac{r_0}{2R} \frac{1 - e^{-\kappa_{\text{on}} r_0/(R\omega)}}{2\pi k_{\text{off}}/\omega + 1 - e^{-\kappa_{\text{on}} r_0/(R\omega)}}.
\]

(A4)

If thermal fluctuations are switched on, there are two important differences. Firstly, the ensemble of trajectories is no longer segregated into ones with favourable or unfavourable initial conditions; all trajectories are statistically equivalent. Secondly, over any single long trajectory, we can distinguish times in which the receptor is bonded, times when it is in the seam and unbonded and times when it is outside the seam and unbonded. In this case,

---

1 This comes from the distribution of waiting times for a Poissonian event: \(\lambda e^{-\lambda t}\). The mean waiting time is \(1/\lambda\). In our case, \(\lambda = k_{\text{off}}\).
therefore,

\[
\langle n_b \rangle = \frac{\tau_{\text{bonded|seam}}}{\tau_{\text{unbonded|non-seam}} + \tau_{\text{unbonded|seam}} + \tau_{\text{bonded|seam}}} = \frac{\tau_{\text{unbonded|seam}}}{\tau_{\text{unbonded|non-seam}} + \tau_{\text{unbonded|seam}} + \tau_{\text{bonded|seam}}} \tag{A6}
\]

At steady state, the equality of probability fluxes into and out of seam regions implies that the fraction of time that the receptor spends on the seam but unbonded is exactly the same as the fractional area of the seam:

\[
\frac{\tau_{\text{unbonded|seam}}}{\tau_{\text{unbonded|non-seam}} + \tau_{\text{unbonded|seam}}} = \frac{r_0}{2R} \tag{A7}
\]

The expressions for \(\tau_{\text{unbonded|seam}}\) and \(\tau_{\text{unbonded|non-seam}}\) derived earlier are still valid. Therefore,

\[
\langle n_b \rangle = \frac{1/k_{\text{off}}}{2R \left( \frac{2\pi}{r_0} \frac{1}{\omega (1-e^{-k_{\text{on}}r_0/(R\omega)})} + 1/k_{\text{off}} \right)} = \frac{2R \frac{2\pi k_{\text{off}}}{r_0}}{\frac{1}{\omega (1-e^{-k_{\text{on}}r_0/(R\omega)})} + 1 - e^{-k_{\text{on}}r_0/(R\omega)}} \tag{A8}
\]

It follows that,

\[
\frac{\langle n_b \rangle_{\text{fluc.}}}{\langle n_b \rangle_{\text{no fluc.}}} = \frac{2\pi k_{\text{off}}/\omega + 1 - e^{-k_{\text{on}}r_0/(R\omega)}}{2\pi k_{\text{off}}/\omega + (1 - e^{-k_{\text{on}}r_0/(R\omega)}) \frac{r_0}{2R}} \tag{A9}
\]
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