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Dynamics of particles with "key-lock" interactions

N. A. Licata and A. V. Tkachenko

Department of Physics and Michigan Center for Theoretical Physics, University of Michigan 450 Church Str., Ann Arbor, MI 48109, USA

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Abstract – The dynamics of particles interacting by key-lock binding of attached biomolecules are studied theoretically. Examples of such systems include DNA-functionalized colloids as well as nanoparticles grafted with antibodies to cell membrane proteins. Depending on the coverage of the functional groups, we predict two distinct regimes. In the *localized regime* at low coverage, the system exhibits an exponential distribution of particle departure times. At higher coverage, there is an interplay between departure dynamics and particle diffusion. This interplay leads to a sharp increase of the departure times, a phenomenon qualitatively similar to *aging* in glassy systems. This *diffusive regime* is analogous to dispersive transport in disordered semiconductors: depending on the interaction parameters, the diffusion behavior ranges from standard diffusion to anomalous, *subdiffusive* behavior. The connection to recent experiments and implications for future studies are discussed.

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Selective key-lock interactions are quintessential for biology. Over the past several years, they have also attracted substantial attention in the context of nanoscience. It is becoming common practice to attach biomolecules capable of key-lock binding to colloidal particles or other microscopic objects to achieve controllable, specific interactions. Examples include nanoparticles functionalized with complementary single-stranded DNA (ssDNA) [1–7], or with antibodies to a particular protein. The possible applications range from self-assembly of smart nanomaterials to biosensors and cell-specific drug delivery [8–10]. In this new class of systems, the collective character of the binding may lead to non-trivial and often prohibitively slow dynamics.

In this letter we report several remarkable results dealing with the dynamics of particles with reversible key-lock interactions. These results are of both conceptual and practical interest. In particular, we will demonstrate that depending on the coverage of the functional groups (*e.g.*, ssDNA or proteins), the system exhibits two distinct regimes. At low coverage, particles are localized on the finite cluster to which they are attached before departing. There is an exponential distribution of departure times, but limited lateral diffusion. If the coverage is sufficiently high, the particle is unable to fully explore the cluster to which it is attached before departing. In this regime the finite cluster behaves effectively as an infinite cluster, and the overall particle dynamics is a result of the interplay between diffusion and desorption. The lateral motion is analogous to *dispersive transport* in disordered semiconductors: it may range from regular diffusion with a renormalized diffusion coefficient, to anomalous, subdiffusive behavior.

In our model, a single particle interacts with a flat two-dimensional surface via multiple key-lock binding (see fig. 1). At each position of the particle, there are m key-lock bridges which may be closed or open, and there is a binding energy ϵ for each of the key-lock pairs (the variation in ϵ is neglected). Therefore, the m-bridge free energy plays the role of an effective local potential for the particle: $U(m) = -k_B T m \Delta$, where $\Delta \equiv \ln(1 + \exp[\epsilon/k_B T])$ [11]. In a generic case, the number of bridges m is a Poisson-distributed random number $P_m = \overline{m}^m \exp(-\overline{m})/m!$, where $\overline{m}$ denotes the mean of the distribution. After staying for some time at a particular site, the particle either breaks all its bridges and departs, or hops a distance a to a new site characterized by a new value for the number of bridges m. In this sense we have coarse-grained the particle motion by discrete steps of the correlation length a, the distance after which the number of bridges becomes statistically independent of the value at the previous location. Below, we calculate the departure time distribution

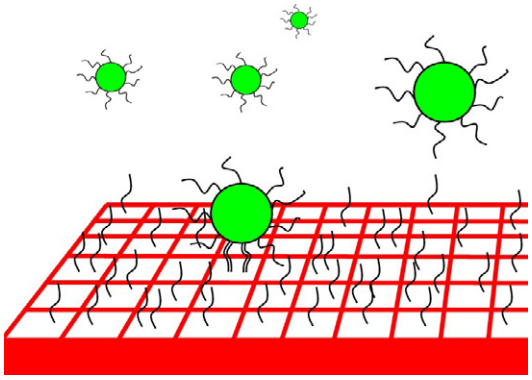

Fig. 1: (Color online) A snapshot of particles interacting with a two-dimensional substrate. Particles are alternately bound to the substrate by bridges, or unbound and free to diffuse in a direction normal to the substrate plane.

$\Phi(t)$ in both the localized and diffusive regimes, provide an estimate of the crossover between the two regimes, and study the random-walk statistics in the diffusive regime.

Diffusive regime. – We first determine the departure time distribution in the diffusive regime, as this regime is typical for all but the sparsest coverage. In the diffusive regime the particle can move around to find a more favorable state on the surface. This leads to a much longer lifetime of the bound state, a phenomenon similar to *aging* in glassy systems. The hopping rate between two neighboring sites is given by the Arrhenius law, $\kappa_{i\to j} = \frac{1}{\tau_0}\exp\left[-\Delta(m_i - m_j)\theta\left(m_i - m_j\right)\right]$. Here $\theta(x)$ is the Heaviside step function, and τ_0 is a characteristic timescale for bridge formation. The problem can be greatly simplified since the ensemble-averaged dwell time τ_m at a site with m bridges can be well approximated by an effective Arrhenius relation:

$$\tau_m = \tau_0 \exp\left[\Delta(m - \overline{m})\right]. \tag{1}$$

In the case when $\Delta\overline{m}$ is sufficiently large, the probability of staying attached to the surface after an n step random walk is $\left(1 - K_m\tau_m\right)^{n-1} = \left[1 - \exp\left(-\Delta\overline{m}\right)\right]^{n-1}$. Here $K_m = \frac{1}{\tau_0}\exp\left(-\Delta m\right)$ is the departure rate from a site with m bridges. It follows that the average number of steps for the random walk is $\langle n\rangle = \exp\left(\Delta\overline{m}\right)$. The departure time distribution $\Phi(t)$ can then be calculated by averaging over the departure time distribution $\phi_n(t)$ for walks with a given n:

$$\Phi(t) = \langle\phi_n(t)\rangle_n. \tag{2}$$

The calculation [12] is simplest in the frequency domain where $\phi_n(\omega) = X(\omega)^n$. Here $Z = 6$ is the coordination number for the triangular lattice:

$$X(\omega) = \left\langle \frac{\tilde{\kappa}}{i\omega + \tilde{\kappa}} \right\rangle_{m,m_1,\cdots,m_Z}, \tag{3}$$

$$\tilde{\kappa} = \sum_{i=1}^{Z} \kappa_{m\to m_i}. \tag{4}$$

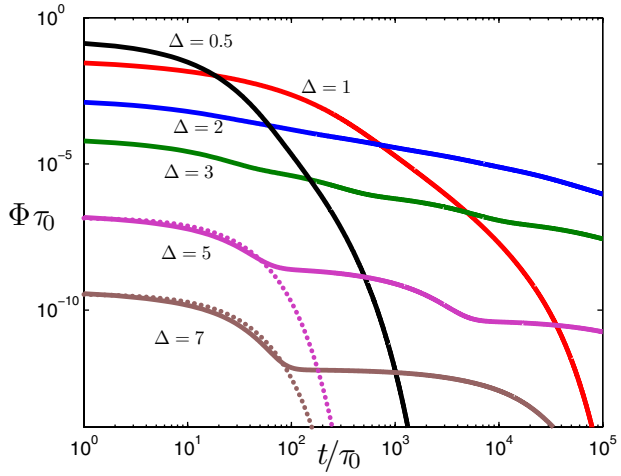

Fig. 2: (Color online) Departure time distribution function *vs.* time with $\overline{m} = 3$. The dotted lines for $\Delta = 5$ and 7 show the exponential approximation $\Phi(t) = K_{\overline{m}}\exp(-\kappa^* t)$.

One can then sum the resulting geometric series for $\Phi(\omega)$ and perform the inverse Fourier transform to derive the following result:

$$\Phi(t) = \exp(\gamma)[\exp(\gamma) - 1]\sum_{r=1}^{\infty}\frac{\exp(-z_r t)}{Y(z_r)}, \tag{5}$$

$$Y(z_r) = i\left.\frac{\mathrm{d}X(\omega)}{\mathrm{d}\omega}\right|_{\omega = iz_r}. \tag{6}$$

Here z_r labels the roots of the equation $\exp(\gamma) - X(iz) = 0$ with $\gamma = -\ln[1 - \exp(-\Delta\overline{m})]$.

We now discuss the behavior of the departure time distribution in several regimes of interest. At fixed $\overline{m}$, for small Δ the behavior is *non-universal*. The departure time distribution exhibits multi-stage behavior, where the initial departure and long-time behavior may both take the shape of a power law, albeit with different exponents (see $\Delta = 0.5$, 1 curves in fig. 2).

As the strength of the key-lock binding increases ($\Delta \gtrsim 1$) there is a crossover from non-universal behavior to *universal power law* behavior for the first several decades in time (see $\Delta = 2$, 3 curves in fig. 2):

$$\Phi(t) \sim t^{-0.7}. \tag{7}$$

For $\Delta \gtrsim 3$ we enter the regime of *multiexponential beating*. The initial departure behavior is well described as an exponential with initial departure rate $K_{\overline{m}} = \exp(-\Delta\overline{m})/\tau_0$ and characteristic timescale $1/\kappa^* \simeq 15\tau_0$:

$$\Phi(t) \simeq K_{\overline{m}}\exp(-\kappa^* t). \tag{8}$$

We attribute κ^* to the diffusive cascade of particles from states with $\overline{m}$ bridges into more highly connected states. Since this process involves particles finding a lower-energy state, κ^* does not depend on Δ. As indicated by the small

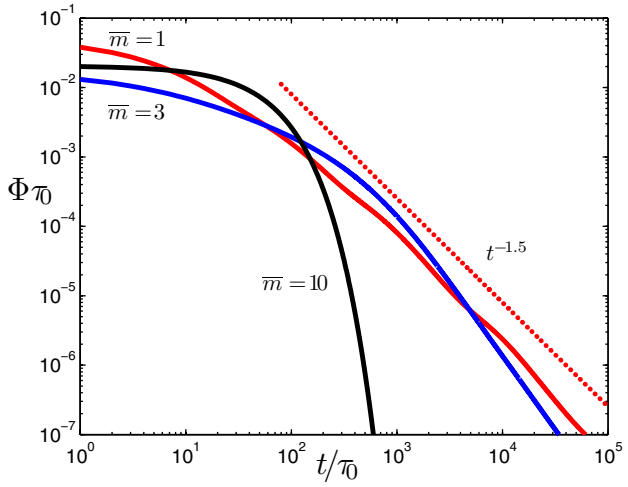

Fig. 3: (Color online) Departure time distribution function *vs.* time with constant average binding energy $\simeq 4k_BT$.

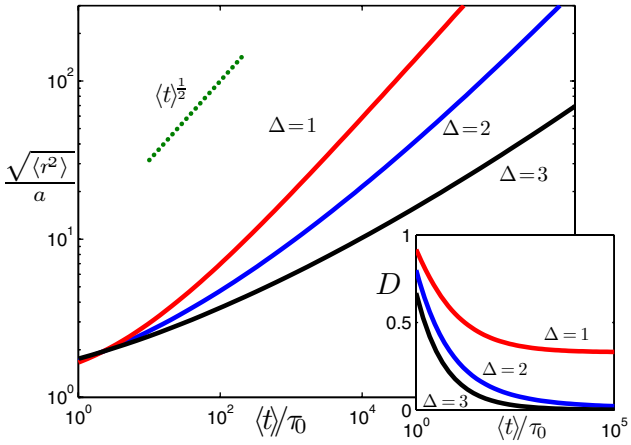

Fig. 4: (Color online) Rms displacement *vs.* time with $\overline{m}=1$. The inset is the dimensionless diffusion coefficient defined as $D=\frac{1}{4D_0}\frac{\partial\langle r^2\rangle}{\partial\langle t\rangle}$ plotted against time.

departure probability, the binding is nearly irreversible in this regime (see $\Delta=5$, 7 curves in fig. 2).

We also plot the departure time distribution relevant to the experimental situation where the average binding energy is held constant [11]:

$$\frac{\Delta\overline{m}}{1-\exp(-\overline{m})}+\ln(1-\exp(-\overline{m}))=\text{const}. \tag{9}$$

The optimal regime for fast departure is to have a large number ($\overline{m}\sim 10$) of weakly bound bridges (see fig. 3). In this fast departure regime the departure time distribution is well approximated as a single exponential, $\Phi(t)=K_{\overline{m}}\exp(-K_{\overline{m}}t)$.

The results of this calculation can be compared to a recent experiment which measured the time-dependent separation of two DNA-grafted particles in an optical trap [1]. In the experiment the tail of the departure time distribution was observed to be a power law $\Phi(t)\sim t^{-1.5}$. A similar behavior is indeed reproduced with a binding free energy of a few k_BT (see $\overline{m}=1$ curve in fig. 3).

Diffusion. – We now discuss the statistics of the in-plane diffusion of the particle. We notice that the in-plane *trajectory* of the particle subjected to a delta-correlated random potential remains statistically equivalent to an unbiased random walk. Therefore, the mean-squared displacement after n steps is given by $\langle r^2\rangle=na^2$. However, as the particle explores the landscape the average hopping time becomes longer and the diffusion gets slower. In the limit $n\to\infty$, the average hopping time can be determined from the equilibrium canonical distribution. Note that to perform this calculation we use the Arrhenius approximation for the dwell times. For the case of Poisson-distributed m, this corresponds to a finite yet renormalized diffusion coefficient D^* with $D_0=a^2/4\tau_0$:

$$D^*\equiv\frac{1}{4}\frac{\partial\langle r^2\rangle}{\partial\langle t\rangle}=D_0\frac{\exp(\Delta\overline{m})\left[\exp(\overline{m})-1\right]}{\exp(\overline{m}e^{\Delta})-1}. \tag{10}$$

However, it may take a very long time to achieve this "ergodic" behavior. In the transient regime, an n-step random walk cannot typically visit sites with an arbitrarily large number of bridges m. Instead, one should average the hopping times only over sites with $m<m^*$. In the language of the statistics of extreme events, m^*-1 is the maximum "expected" value of m in a sample of n independent events [13]. Both the average diffusion time $\langle t\rangle$, and mean square displacement $\langle r^2\rangle=na^2$, can be expressed in terms of m^*, which defines their relationship in parametric form:

$$\langle r^2\rangle=\frac{a^2}{P(\overline{m},m^*)}, \tag{11}$$

$$\langle t\rangle=\frac{\langle r^2\rangle}{D^*}\left(1-\frac{P(\overline{m}e^{\Delta},m^*)}{1-\exp\left(-\overline{m}e^{\Delta}\right)}\right). \tag{12}$$

Here $P(x,m^*)\equiv\gamma(x,m^*)/\Gamma(m^*)=\exp(-x)\sum_{k=m^*}^{\infty}x^k/k!$ is the regularized lower incomplete Γ-function. It is easy to see that in the limit $m^*\to\infty$ we recover the renormalized diffusion relation $\langle t\rangle=\langle r^2\rangle/D^*$. However, this generally occurs after a very long time which is not accessible experimentally. In the transient regime we expect anomalous, subdiffusive behavior. As shown in fig. 4, this regime is typical for strong enough key-lock interactions. By approximating the incomplete gamma functions, the transient behavior may be well described by a power law with a single free parameter $\beta\simeq 0.15$ (see fig. 5):

$$\frac{\langle r^2\rangle^{\frac{1}{2}}}{a}\simeq\left(\frac{\langle t\rangle}{\tau_0}\right)^{\eta}, \tag{13}$$

$$\eta=\frac{1}{2}-\frac{1+[\Delta-1]\exp(\Delta)}{2\Delta[\exp(\Delta)-1]-\frac{2}{\beta\overline{m}}\ln\left[1-\exp(-\beta\overline{m})\right]}. \tag{14}$$

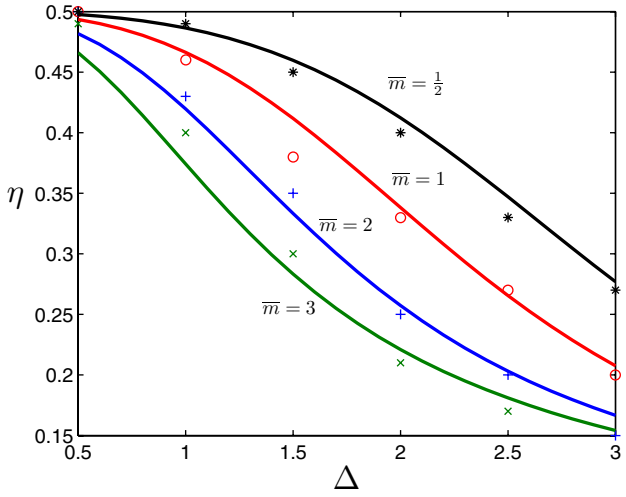

Fig. 5: (Color online) Comparison of the power law exponent determined numerically to eq. (14) in the transient regime.

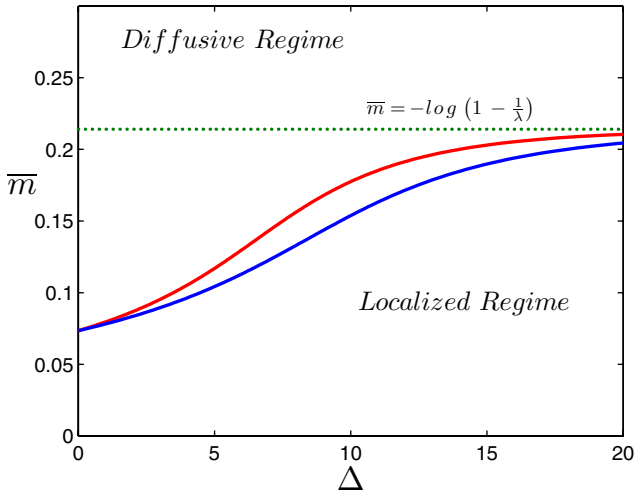

Fig. 6: (Color online) The crossover from the localized to diffusive regime occurs below the percolation threshold $\overline{m} = \ln 2$. For large Δ the crossover condition is $\overline{m} = -\ln\left(1 - \frac{1}{\lambda}\right)$.

Crossover. – As the coverage is reduced, the lateral diffusion of the particle is limited, and particles enter the localized regime. In the localized regime the particle remains close to the original location until breaking all its bridges and departing. Note that the crossover from the diffusive to localized regime occurs at lower coverage than the percolation threshold where one first encounters an infinitely connected cluster of sites with $m > 0$. For site percolation on the triangular lattice the percolation transition occurs at $\overline{m} = \ln 2$. The first estimate for the location of the crossover is obtained by comparing the average number of steps for the random walk $\langle n \rangle = \exp(\Delta \overline{m})$ to the characteristic cluster size $s_c = 1/\ln(1/\lambda p)$ below the percolation threshold. The numerical constant $\lambda = 5.19$ for the triangular lattice, and for the Poisson-distributed bridge numbers the occupancy probability $p = 1 - \exp(-\overline{m})$. The crossover condition $\langle n \rangle = s_c$ can be expressed as

$$\Delta = -\frac{1}{\overline{m}} \ln\left[-\ln\left\{\lambda\left(1 - e^{-\overline{m}}\right)\right\}\right]. \tag{15}$$

To provide an alternative estimate we consider the confinement of the particle's random walk by the radius of gyration of the characteristic cluster. Below percolation, the radius of gyration of the cluster is $R_s \sim s^\rho$ where $\rho = 0.641$ in two dimensions. By comparison to the radius of gyration for the particle's random walk $\langle n \rangle^{\frac{1}{2}}$, the crossover condition is $\langle n \rangle^{\frac{1}{2}} = (s_c)^\rho$. The values 2ρ and 1 differ by less than 30%, so both conditions give similar crossovers (see fig. 6).

Localized regime. – Well below the percolation threshold a particle is thermalized, *i.e.* it fully explores the finite cluster to which it is attached before departing. The departure rate is given by the Arrhenius relation $K = \frac{1}{\tau_0} \exp\left(\frac{F}{k_B T}\right)$. The probability that the particle departs from the surface between time t and $t + \mathrm{d}t$ is $\Phi(t)\mathrm{d}t = K\exp[-Kt]\mathrm{d}t$. In this regime we can calculate the cluster free energy $F = -k_B T \ln\langle Z \rangle$ by averaging the partition function for the finite clusters. Since this regime is not typical, and the results can be accurately approximated in much simpler form, we omit the details of the calculation. The interested reader is directed to ref. [12].

In the localized regime with very low coverage, the characteristic cluster size $s_c \simeq 1$ and the departure time distribution is accurately approximated as a single exponential with departure rate $k = \exp(-\Delta)/\tau_0$:

$$\Phi(t) = k \exp(-kt). \tag{16}$$

In fig. 7 the departure time distribution is plotted in the localized regime. As indicated in the plot, increasing Δ decreases the rate of particle departure.

Experiment. – This work provides additional insight into the slow crystallization dynamics of key-locking particles (see fig. 8). Recent experimental studies demonstrated that micron diameter particles grafted with ssDNA form reversible aggregates. The resulting structures were mainly disordered aggregates [2], or random hexagonal close-packed crystals [1]. Controlled colloidal crystallization into the various phases predicted theoretically [14] remains elusive. Crystallization requires that colloids repeatedly depart and reattach to the growing structure, in an effort to find their desired lattice location [15].

We can attempt to quantify this optimal experimental regime of fast departure by determining the time T_{dep} required for 90% of the particles to depart: $0.1 = \int_{T_{dep}}^{\infty} \Phi(t)\mathrm{d}t$. Figure 9 is a plot of T_{dep} *vs.* $\overline{m}$ at constant binding free energy. The optimal regime is to have a large number ($\overline{m} \sim 10$) of weakly bound bridges. For comparison we have also plotted the time T_{dif} required for the particle to diffuse along the surface of a particle to which it is

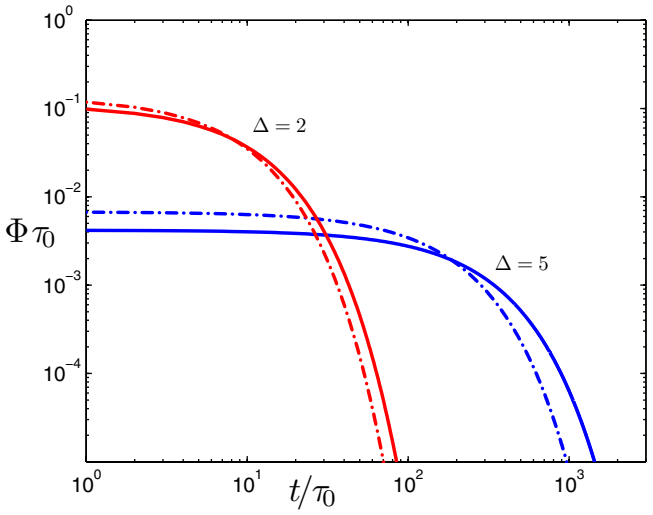

Fig. 7: (Color online) Departure time distribution function *vs.* time in the localized regime (solid lines) at $\overline{m} = 0.1$. For comparison the dash-dotted curves are the exponential relaxation $\Phi(t) = k \exp(-kt)$ with departure rate $k = \exp(-\Delta)/\tau_0$.

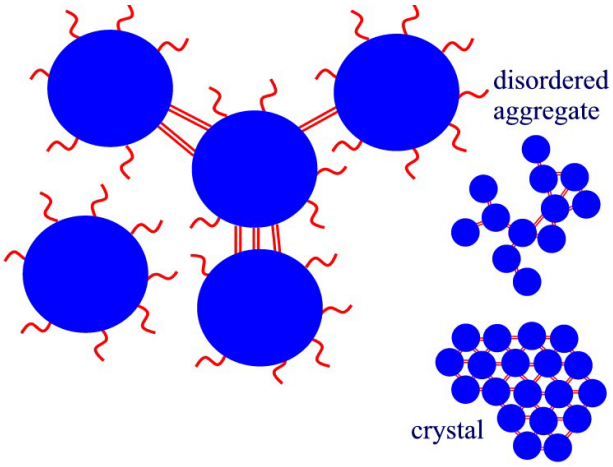

Fig. 8: (Color online) Schematic depiction of key-lock binding between nanoparticles functionalized with complementary ssDNA. The resulting structures can be disordered, fractal-like aggregates, or crystalline.

attached. Since $T_{dif} > T_{dep}$, in the DNA-colloidal system departure and reattachment is the dominant mechanism for relaxation, as opposed to surface diffusion.

To realize this regime experimentally we propose the introduction of long, flexible DNA linkers to a system of particles with a high coverage of short ssDNA. This scheme increases the number of key-lock bridges between particle pairs as compared to previous experiments, and therefore has the potential to substantially reduce the time required for crystallization.

Conclusions. – In this work we studied the dynamics of particles which form multiple, reversible key-lock bridges. There is a crossover which separates the regime in which particles are localized near their original

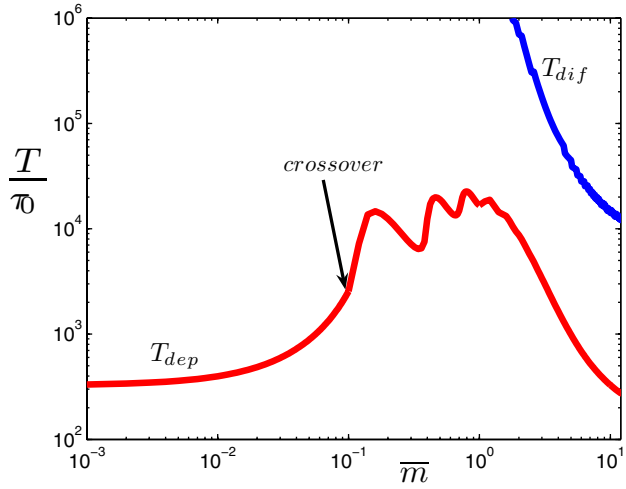

Fig. 9: (Color online) Plot of the time T_{dep} required for 90% of the particles to depart *vs.* $\overline{m}$.

location from the regime where they exhibit diffusive behavior by breaking and reforming bridges. At low coverage the key-locking system exhibits an exponential distribution of departure times, and particles remain localized on the finite cluster to which they first attach. Above the crossover diffusion allows the particle to cascade into deeper energy wells with a large number of key-lock bridges. This leads to an increase in the bound-state lifetime similar to *aging* in glassy systems. The statistics for the particles' in-plane diffusion were determined. For relatively weak key-lock interactions there is a finite renormalization of the diffusion coefficient. However, as Δ increases, the system exhibits anomalous, sub-diffusive behavior analogous to dispersive transport in disordered semiconductors. We discussed the connection between our work and recent experiments with DNA-coated colloids. The findings indicate that the optimal regime for colloidal crystallization, where particle departure is a relatively fast process, is to have a large number of weakly bound key-lock bridges.

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