Effect of Contact Inhibition Location on confined cellular organization

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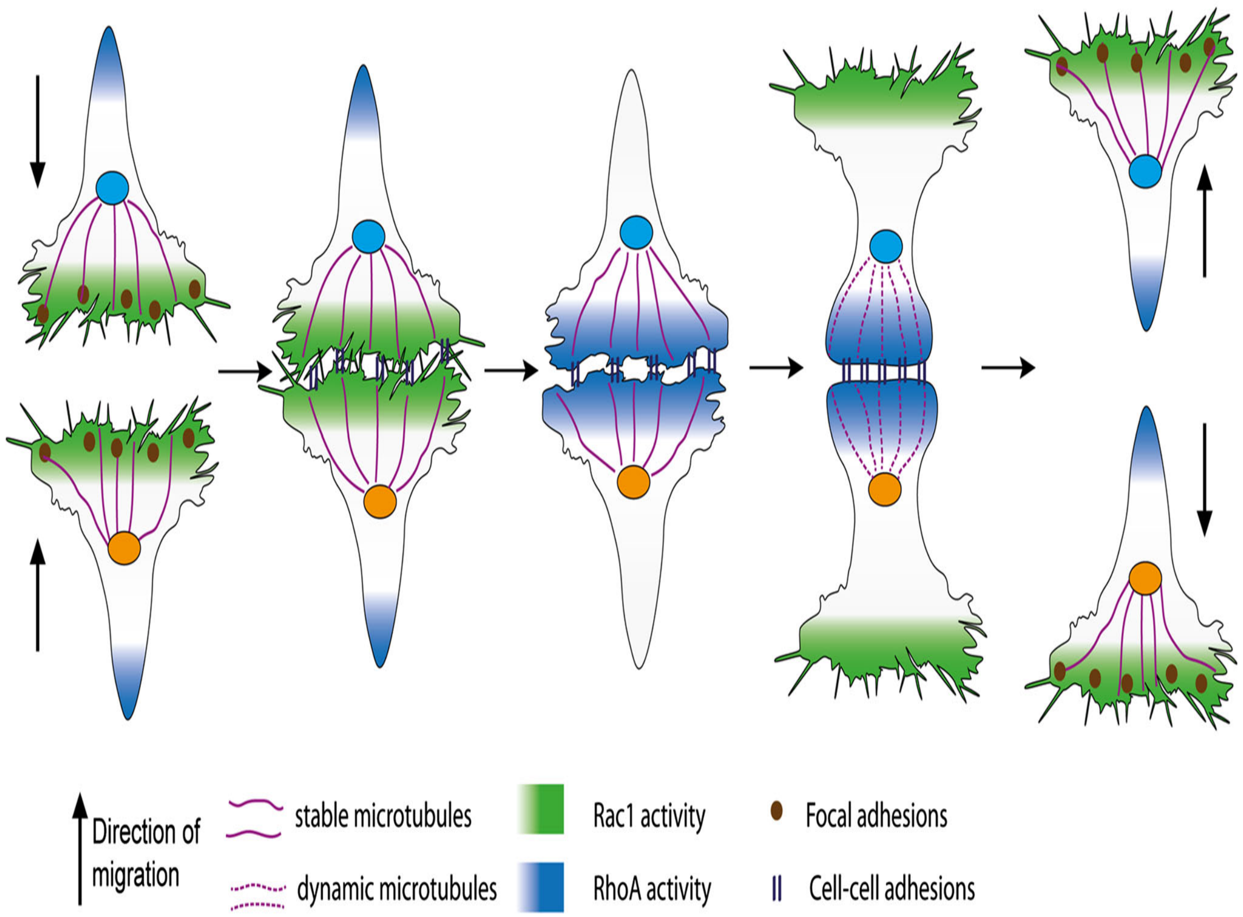
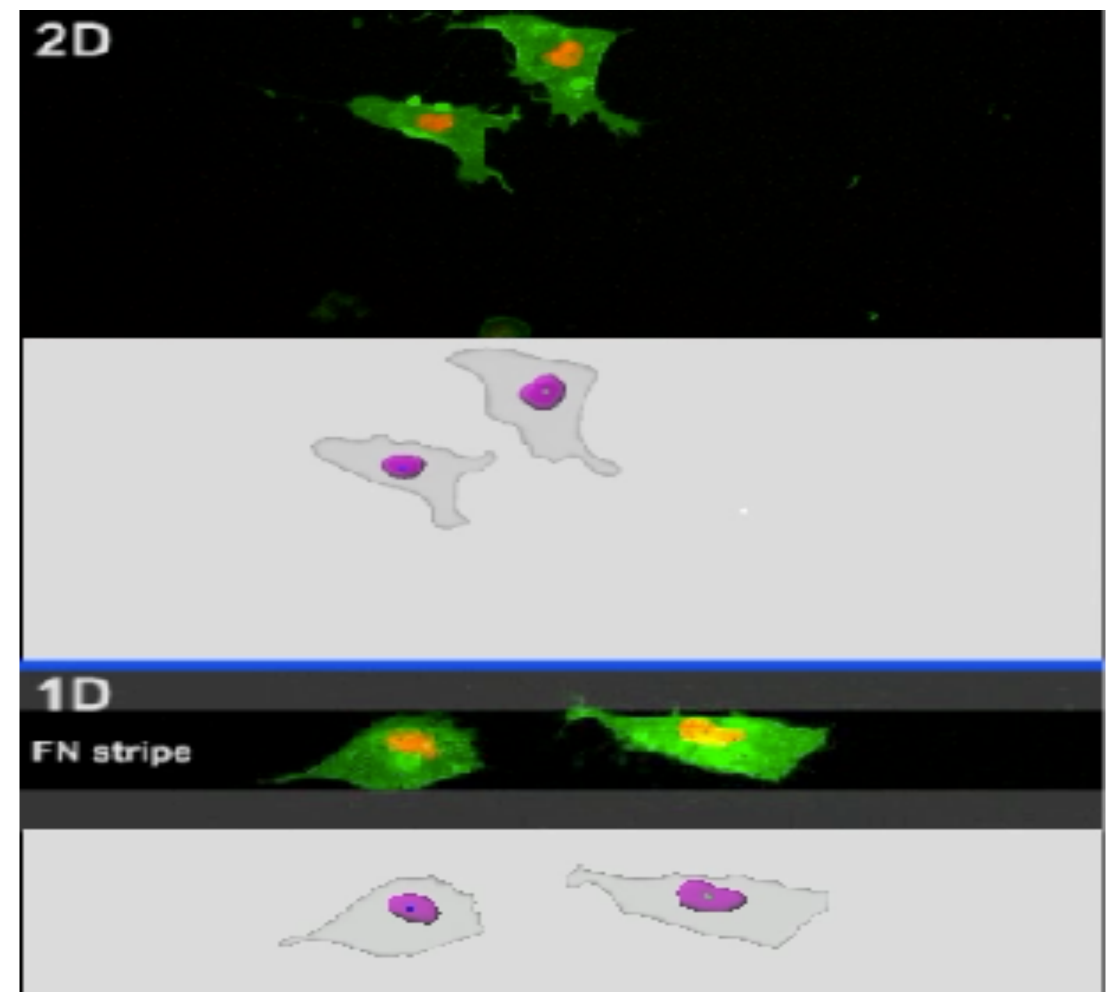
Contact Inhibition Location (CIL)

CIL : Directional reorientation of migrating cells when they come in contact with other cells



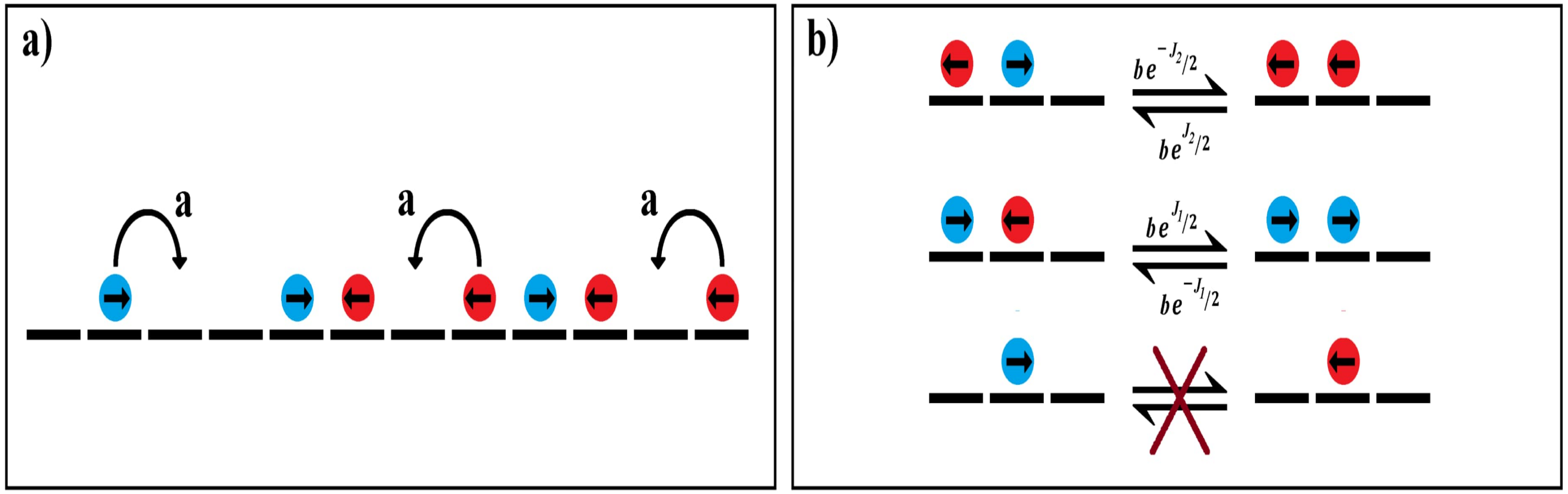
A. Roycroft & R. Mayor, Cell. Mol. Life Sci. 73, 1119 (2016)



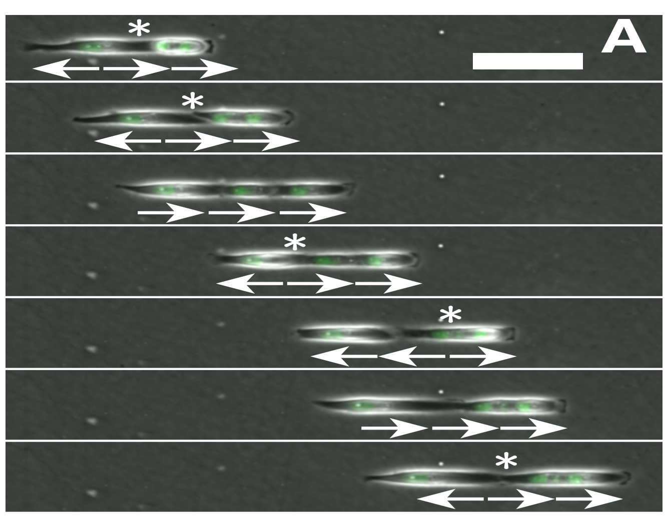
Cell migration on fibronectin coated 1D substrate

(E. Scarpa at.al, Biol. Open, 2, 901, 2016)

Model to study effect of CIL on cellular organization in 1D



CIL interaction between particles: $H = \sum_i J_1 \Theta(\sigma_i - \sigma_{i+1}) - J_2 \Theta(\sigma_{i+1} - \sigma_i)$



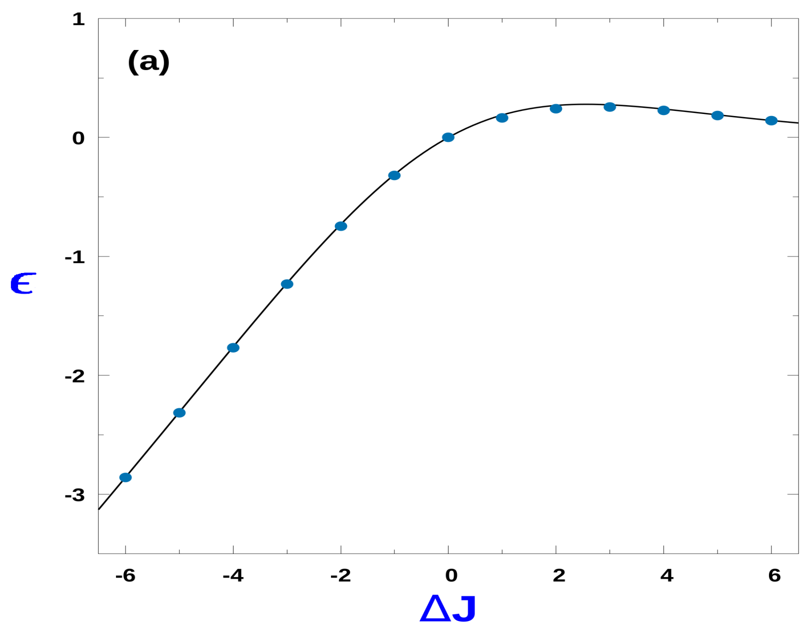
$$
\begin{array}{llll}
\rightarrow \;\; \leftarrow & \equiv & E = +J_1 & (J_1 > 0) \\
\leftarrow \;\; \rightarrow & \equiv & E = -J_2 & (J_2 > 0) \\
\rightarrow \;\; \rightarrow & \equiv & E = 0 & \\
\leftarrow \;\; \leftarrow & \equiv & E = 0 &
\end{array}
$$

T. Bertrand. et.al, arXiv 2012.00785

Confluent state: A reduced equilibrium model

- **When all the adherent cells fill the fibronectin coated strip, it corresponds to a confluent state**
- **In confluent state, there are no vacancies in the lattice and there is no translation dynamics**
- **The dynamics is restricted to switching process between different states of polarization of the particles.**

Average Energy: $$\langle E\rangle = \frac{N\Delta J}{2}\left[\frac{1}{1+\exp(\Delta J/2)}\right] \text{ where } \Delta J = J_1 - J_2$$

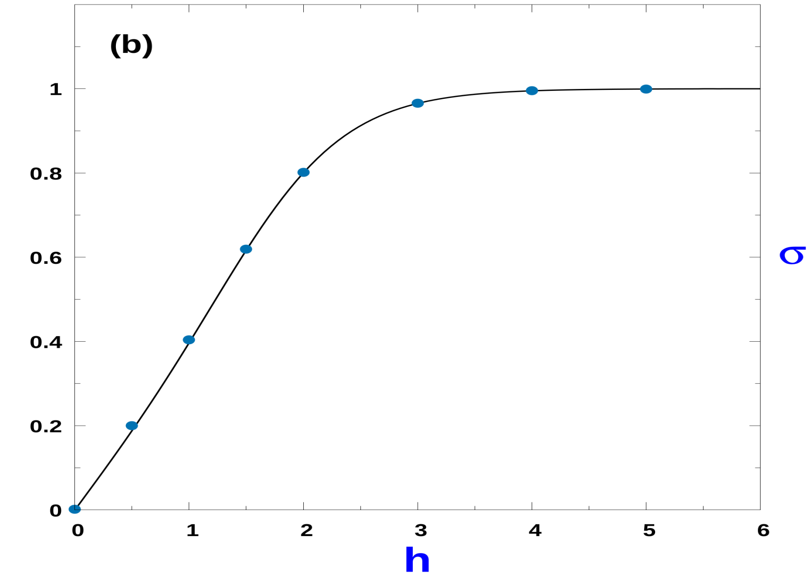


Correlation function: $$G(r) = \left(\frac{1-\exp(-\Delta J/2)}{1+\exp(-\Delta J/2)}\right)^r$$

In the limit of $\exp(\Delta J/2) >> 1$, the correlation length $\xi \to \frac{1}{2}\exp(\Delta J/2)$

For an external field h which couples to polarization ,

Av. Polarization: $$m = \frac{Sinh(h)}{[Cosh^2(h) + e^{-\Delta J} - 1]^{1/2}}$$



Dynamics & clustering in presence of vacancies

Q = a / b : Ratio of hopping and switching rate

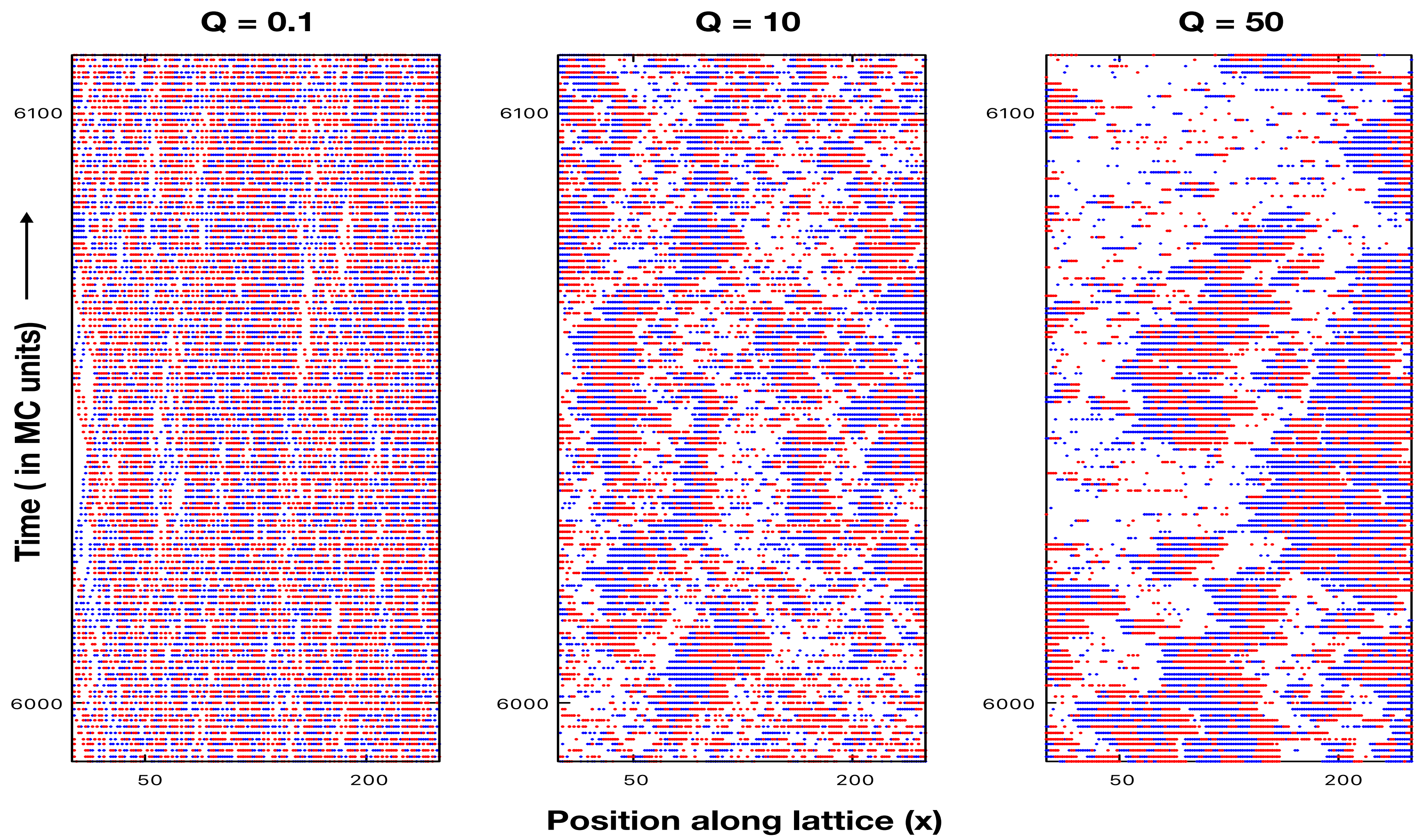


FIG. 3. Spatio-temporal plot: Time snapshots of distribution of right polarized (+)(blue) and left polarized (−)(red) particles on the lattice. Here $Q = 0.1, 10, 50$, $J_1 = 4$, $J_2 = 0$, with $\rho = 0.6$. MC simulations where done with $L = 1000$

Cluster Size distribution

When $Q << 1$: $P(m) = \left(\frac{1-\rho}{\rho}\right) e^{-m/\xi}$ **(Identical for SEP or TASEP)**

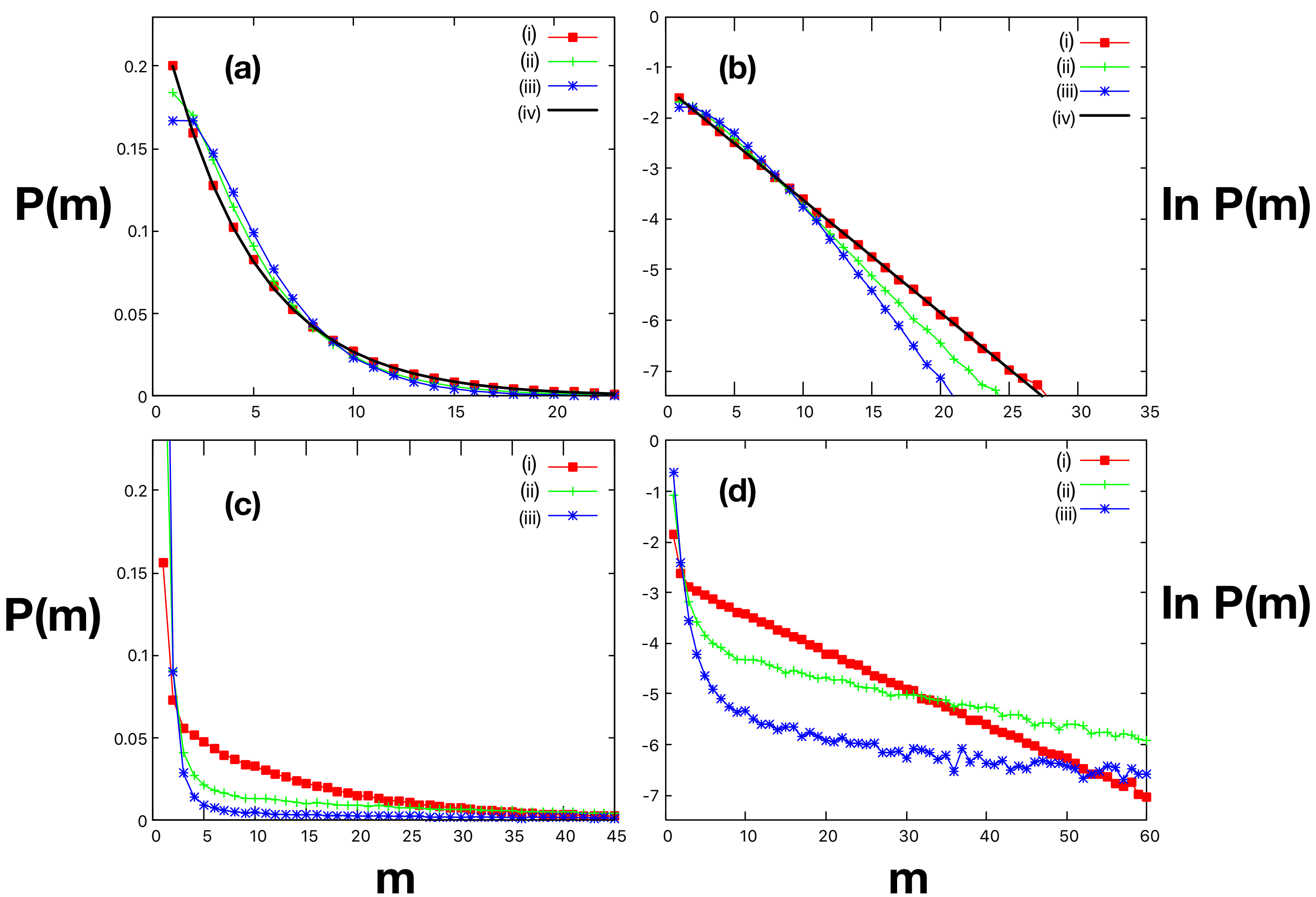
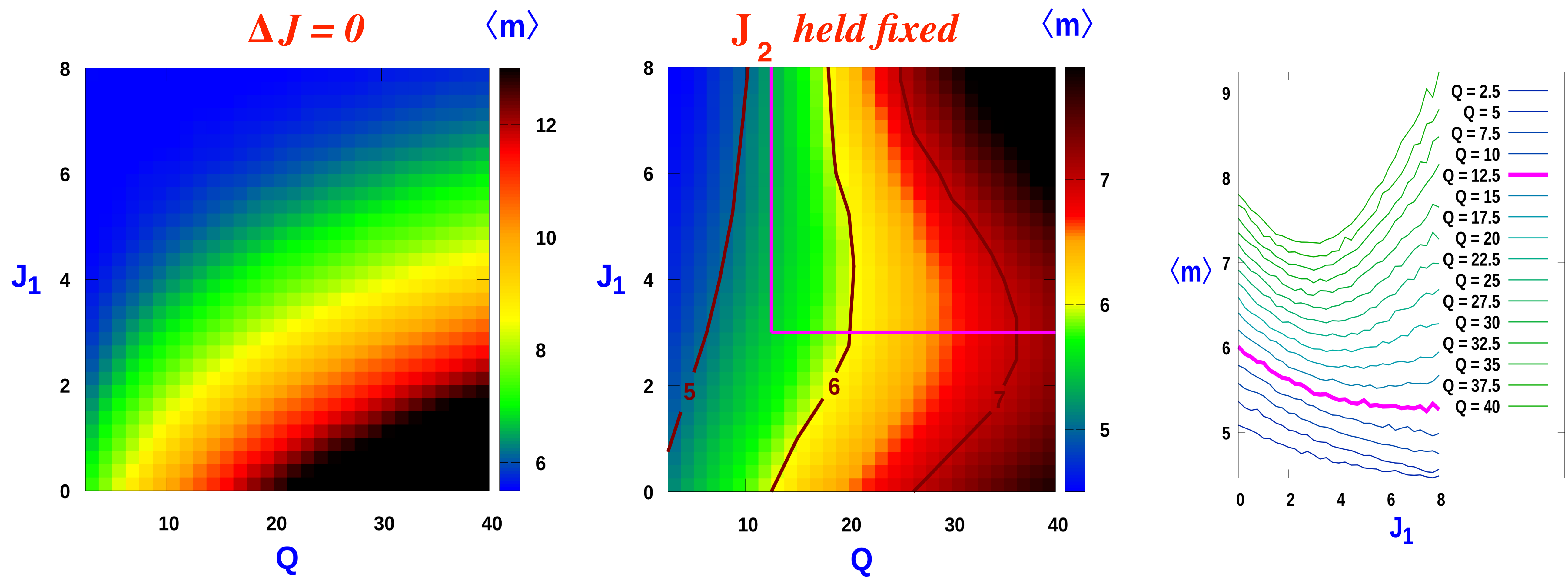


FIG. 4. (a) Probability distribution of cluster size (m) in low Q limit ($Q = 0.1$) for different CIL strength: (i) $J_1 = 0.1$, (ii) $J_1 = 3$, (iii)$J_1 = 7$, (iv) Eq.11 (PDF for TASEP). (b) logplot corresponding to (a). (c) Probability distribution of cluster size (m) in high Q limit ($Q = 30$) for different CIL strength: (i) $J_1 = 0.1$, (ii) $J_1 = 3$, (iii)$J_1 = 7$. (d) logplot corresponding to (c). For all cases, $J_2 = 0$, $\rho = 0.8$, $N = 1000$. MC simulations are performed and averaging is done over 2500 samples.

Contour map of variation of mean cluster size $\langle m \rangle$ with ΔJ and Q



- System exhibits 're-entrant' behavior for cluster size as function of $J1$ when $\Delta J \neq 0$

Increasing CIL may increase av. Cluster size !

- For $Q >> 1$ limit, the average cluster size $\langle m \rangle \sim Q^{1/2}$

- Average cluster size is a monotonically increasing function of Q

Mapping to an equivalent equilibrium process when Q >> 1

- The system comprises of alternate regions of dense Cluster phase (c) & low density gas (g) phase.
- In this limit inter cluster interaction is weak and they evolve independently.
- Problem gets mapped to an equivalent equilibrium process for the sizes of clusters.
- Cluster size distribution is obtained by minimization of Helmholtz Free Energy

Average energy : $\langle E(l) \rangle = \frac{l}{2}\left[\frac{J_1}{1+e^{J_1/2}}\right]$, when $J_2 = 0$

Configurational Entropy: $S = ln\left[\frac{C\,!}{\prod_l G_c(l)!}\right] - \lambda\left(N_c - \sum_l lG_c(l)\right) - \gamma\left(C - \sum_l G_c(l)\right)$

N_c = # of particles in c phase

G_c = # of clusters of size l

C = # of clusters

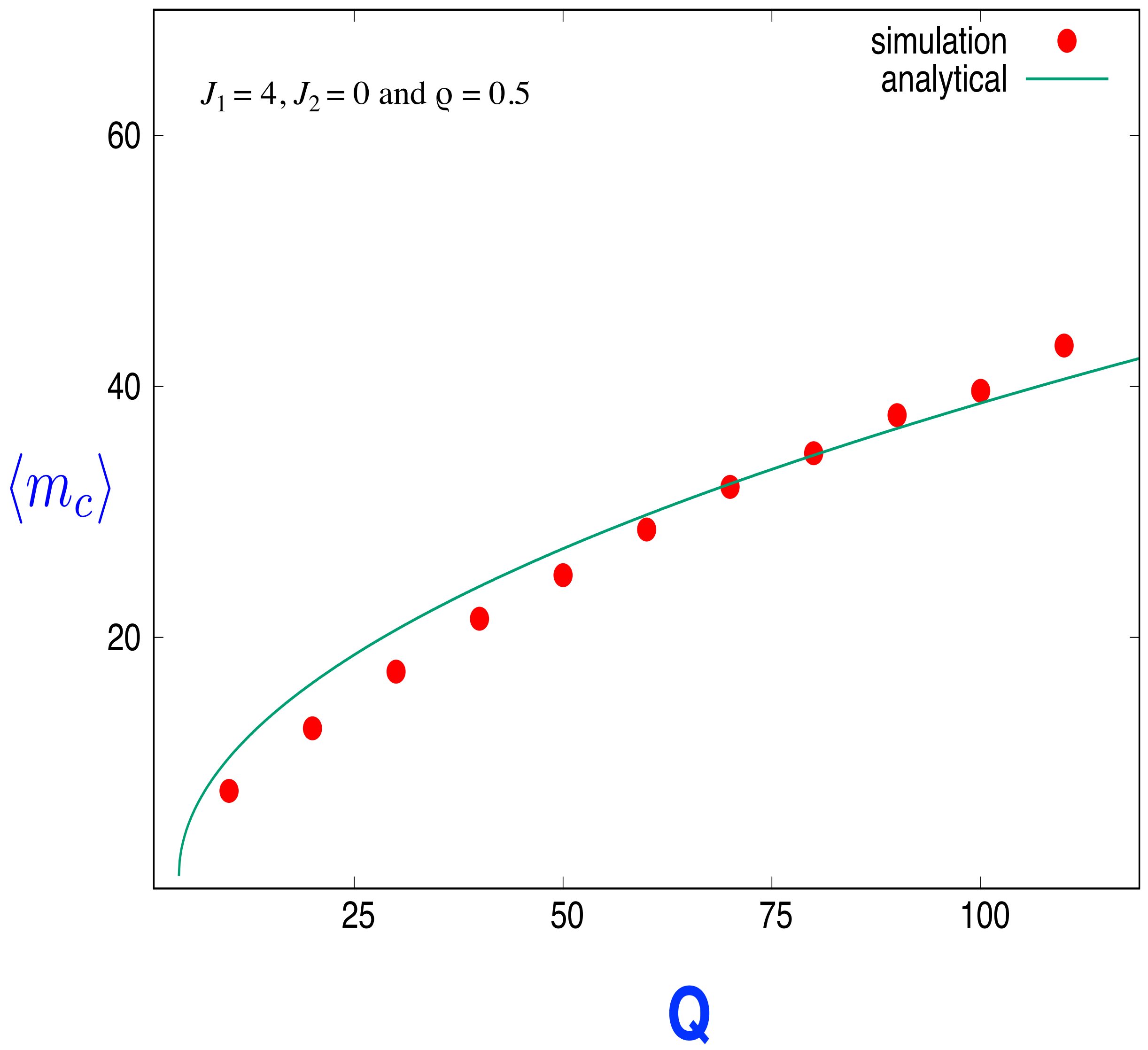
Helmholtz Free energy

$$F = \left[\frac{J_1/2}{1+e^{J_1/2}}\right]\sum_l lG_c(l) - ln\left[\frac{C\,!}{\prod_l G_c(l)!}\right] + \lambda\left(N_c - \sum_l lG_c(l)\right) + \gamma\left(C - \sum_l G_c(l)\right)$$

Approximate expression for average cluster size

$$\langle m_c \rangle = 1 + \sqrt{1 + 2Q\left(\frac{\rho - 2/Q}{1-\rho}\right) e^{J_1/2}}$$

- **Average cluster size** $\sim \sqrt{Q}$



Polarization characteristics within Cluster

$$S_F = \frac{1}{m}\sqrt{\overline{\left(\sum_{i=1}^{m}\sigma_i\right)^2}}$$

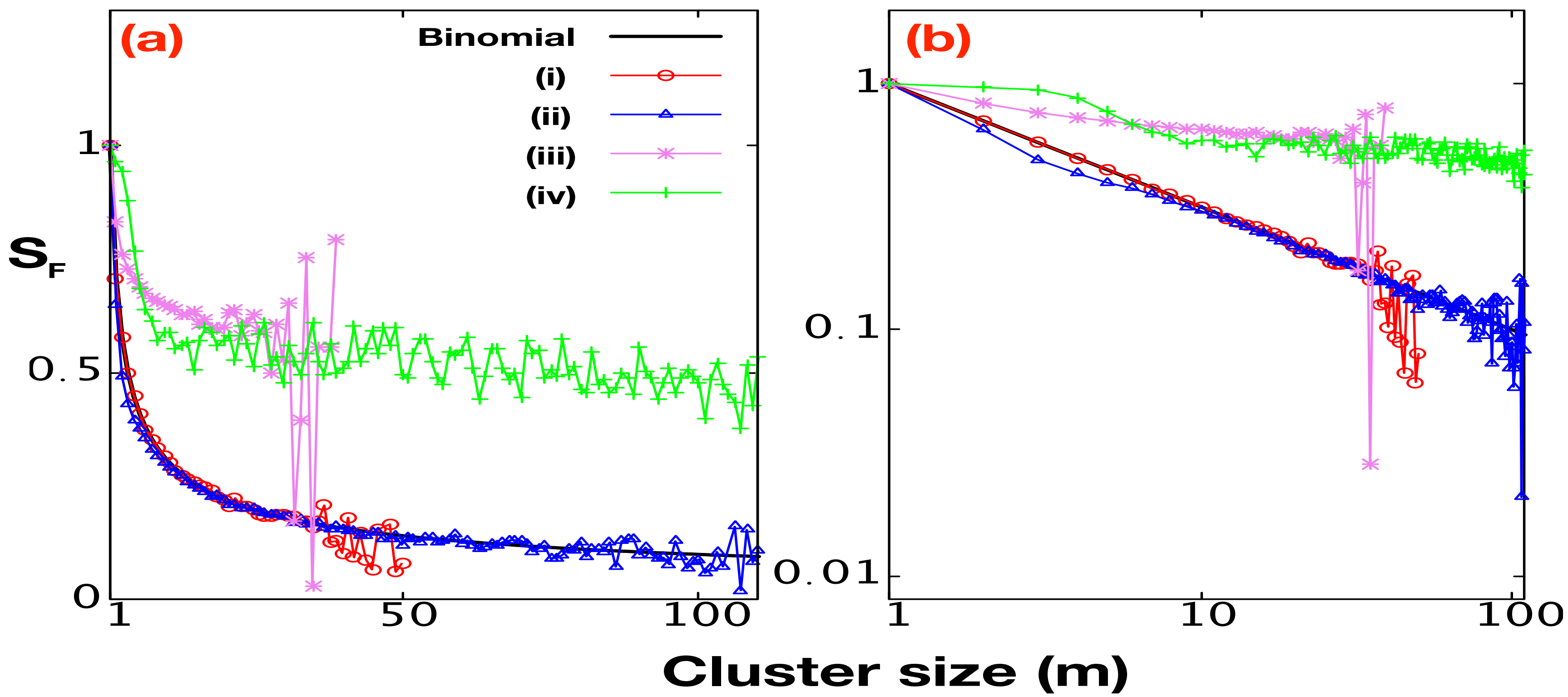


Figure 7. (a) Plot of RMS Fluctuation of Polarization in a cluster of size m (S_F) vs Cluster size (m) : (i) No CIL and low Q ($Q = 0.1$), (ii) No CIL and high Q ($Q = 30$), (iii) $J_1 = 7$ and low Q ($Q = 0.1$) , (iv) $J_1 = 7$, high Q ($Q = 30$). The binomial distribution corresponds to solid black line. (b) The corresponding log-log plot for (a). Here $J_2 = 0$, with $\rho = 0.8$. MC simulations where done with $L = 1000$ and averaging was done over 2000 samples.

Effect of external field on cluster characteristics

- **The hopping rate of the (→) particle becomes $a + h$, while for (←) particles, hopping rate is $a - h$**

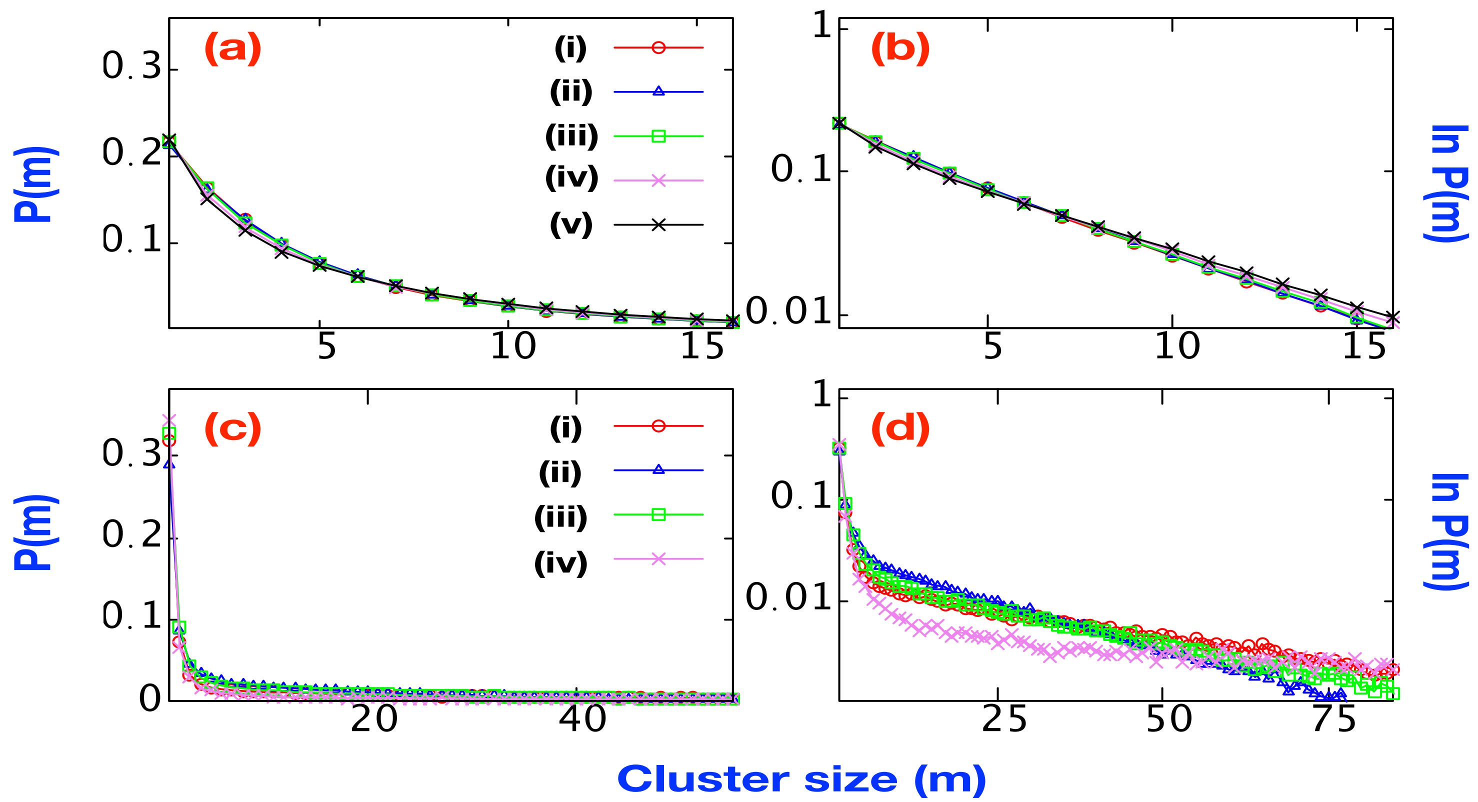


Figure 9. (a) Plot of Cluster size distribution function for low Q (Q = 1) with $a = 1$: (i) h = 0, (ii) h = 0.2, (iii) h = 0.5, (iv) h = 0.9, (v) h = 1. (b) The corresponding logplot for (a). (c) Plot of Cluster size distribution function for high Q (Q = 50) with $a = 50$: (i) h = 0, (ii) h = 25, (iii) h = 40, (iv) h = 50. (d) The corresponding logplot for (c). Here $J_1 = 3$, $J_2 = 0$ and $\rho = 0.8$. MC simulations where done with $L = 1000$ and averaging was done over 2000 samples.

- **Average cluster size varies non-monotically on increasing *h***
- **As *h* approaches the hopping rate *a*, average cluster size sharply increases.**

CONCLUSION & OUTLOOK

- For the confluent state (no vacancies), an exactly solvable model discussed
- Average cluster size depends non-monotically on CIL strength.
- Corresponding contour plot exhibits a ‘re-entrant’ like behavior.
- For Q >> 1 limit, an approximate expression for average cluster size obtained.
- We do not observe any MIPS transition

- How does interplay of CIL with cell-cell adhesion and alignment manifest itself ?
- Generalization to 2D, and comparison with Continuum Hydrodynamic models.

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