

# Bacterial aggregation in the presence of directed motion

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We model directed motion of cells that aggregate into a cluster in the presence of chemotaxis or fluid transport. Starting from a stochastic agent-based model (ABM) of Galante & Levy (2013), Chavy-Waddy & Kolokolnikov (2016), we consider two model variants, with (I) directed motion of individuals, or (II) implicit individual bias in one direction. In both cases, we derive fourth order nonlinear PDEs representing the continuum limits of the models as a generalization of Chavy-Waddy & Kolokolnikov (2016). An exact analytic solution then describes cluster density profile as well as the group velocity, and we identify the regimes where the travelling cluster exists. Excellent agreement is observed between the discrete models and the exact solutions of the PDEs in both models, including the existence and speed of the travelling cluster.

## 1. INTRODUCTION

In a series of papers [1–5], the authors proposed several models of motion of cyanobacteria *Synechocystis sp.* Two key aspects were emphasized: aggregation – localized areas of high bacterial density; and the motion towards a light source (phototaxis). While phototaxis is induced by a light gradient, bacterial aggregation can happen even in the absence of such gradient [1, 5].

Models for collective motion of cells date back to the 1970’s with the classic Keller-Segel model [6] for traveling bands of chemotactic bacteria, moving up a nutrient gradient. In [7], the approximate shape of the cell density profile was derived from a similar continuum model. More recently, chemotactic *E. coli* were tracked experimentally in micro channels and compared with a one-dimensional (1D) continuum model [8]. Indeed, the development of micro fluidic devices [9] and adhesive patterns has enhanced the ability to measure cell motion and cell interaction in simplified system geometry. Such experiments also extend to mammalian cells, though typically with smaller cell populations. Chemotaxis and cell pair interactions were quantified in 1D microfluidic device by [10], and interactions of “trains” of cells on 1D adhesive strips were observed in [11]. Observations in vivo of embryo development reveal that neural crest cells become polarized, attract one another, and migrate to target sites with directional preference [12–14]. In some cases, e.g. the development of the lateral line in zebrafish, a group of roughly 100 cells migrates along a 1D track in a polarized cluster [15]. Such studies motivate our goal of understanding how the motion of cells is influenced by external bias, cell-cell interactions, fluid flow in the environment, and directional cues. In contrast to other modeling studies where multiple cell types and signals are considered, we here consider a minimal 1-cell-type model with basic cell-cell interactions to determine conditions for cohesive group motion.

Numerous other models of bacterial aggregation have been proposed. There is a very large literature on this topic, often referred to as collective motion; here we mention just a few representative studies. This includes Langevin-type nonlocal models, [16–19], reaction-diffusion models [20, 21], cellular automata models [22, 23], state-dependent diffusion [24], and correlated random walk models [25, 26].

In [5] the authors derived a fourth order nonlinear PDE in the continuum limit, which exhibits localized spikes corresponding to the clusters observed in the discrete model from [1], in the absence of light gradient. In this paper we extend the work from [5] by introducing two different mechanisms that induce the cluster motion. These are:

- (I) A transport velocity, for example, due to fluid flow.
- (II) Biased direction selection, such as a bias towards a source of light or a chemical gradient.

For both models, we analytically derive the aggregation profile using a variant of the method first proposed in [5]. In addition to the profile shape, this method also yields an exact analytical expression for the speed of spike motion, as a function of model parameters. We further determine the parameter regime in which such a travelling cluster exists including a region of bistability in model II where a homogeneous and cluster solution coexist.

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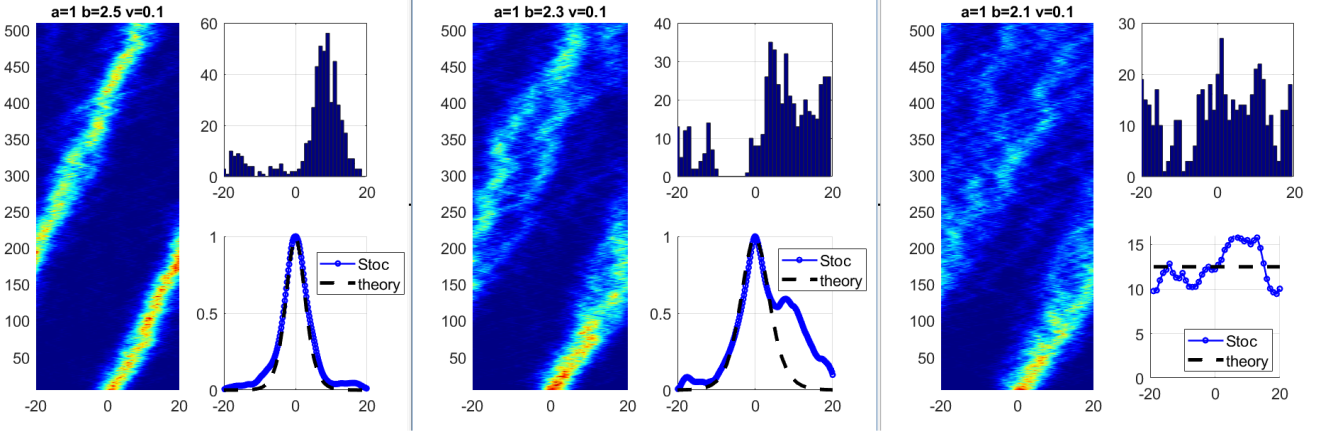


FIG. 1. Three distinct simulations of the stochastic ABM version of Model I on a periodic domain with  $n = 1000$  particles. and for parameters as given. For each of three panels, left is a time-space plot (kymograph) of the particle density. Top right is a histogram of particle locations at  $t = 500$ . Bottom right shows the average profile of the moving cluster (histogram averaged over  $t = 300 \dots 500$ ), normalized to center the distribution at  $x = 0$ . Overlaid is the theoretical prediction given in (2.17). In all simulations we took  $d = 1$ . For the third simulation, the aggregation parameter  $b$  is exactly at the threshold  $b_c = 2a + v$  and the cluster dissipates.

## 2. MODEL I: DIRECTED MOTION

At an agent-based level, the model description is as follows. Each individual has three components of motion

1. Random: with a rate of  $2a \cdot dt$ , a cell moves one step either left or right.
2. Aggregation: With a rate of  $b \cdot dt$ , the cell randomly chooses a neighbour within its sensing radius  $d$ . It then moves one step towards that neighbour.
3. Directed motion: with a rate  $v \cdot dt$ , the cell is transported one step to the right.

Note that this model (with  $v = 0$ ) is a simplification of the model introduced in [1, 5]. There, each particle remembers its past direction. By contrast here, we consider a simpler model where a new direction is chosen at every time-step.

It was previously observed that for sufficiently large aggregation rate  $b$ , the particles start to cluster [1, 5]. Conversely, we find that the cluster starts to dissipate if either the velocity  $v$  or random motion rate  $2a$  is increased too much. A sample simulation demonstrating these effects within the stochastic model above is shown in Figure 1.

In the limit of a large number of particles, we discretize the space into  $N$  bins and let  $U_j$  be the particle density within the bin  $j$ . Figure 2 shows the transition diagram between different bins. Taking the limit  $dt \rightarrow 0$ , the agent-based model reduces to an ODE system,

$$\frac{dU_j}{dt} = a(U_{j-1} - 2U_j + U_{j+1}) + b(\eta_{j+1}^- U_{j+1} - U_j + \eta_{j-1}^+ U_{j-1}) + v(U_{j-1} - U_j); \quad (2.1)$$

$$\eta_j^\pm = \frac{\sum_{k=1}^d U_{j \pm k}}{\sum_{k=1}^d (U_{j+k} + U_{j-k})}. \quad (2.2)$$

Here,  $\eta_j^-$  and  $\eta_j^+$  correspond to the fraction of particles either to the left (-) or to the right (+) of bin  $j$ , within a sensing distance  $d$ .

In the limit of a large number of bins, the model (2.1) reduces to a PDE that we now derive. Approximate  $U_j(t) \sim u(x, t)$  where  $x = jh$ , and  $h$  is the spacing between the bins, assumed to be small. Using a Taylor series expansion in  $h$ , following the procedure in [5], expanding to two orders we obtain the approximation

$$u_t = -\frac{h^2}{2}(bd - 2a - v)u_{xx}(x, t) - vhu_x(x, t). \quad (2.3)$$

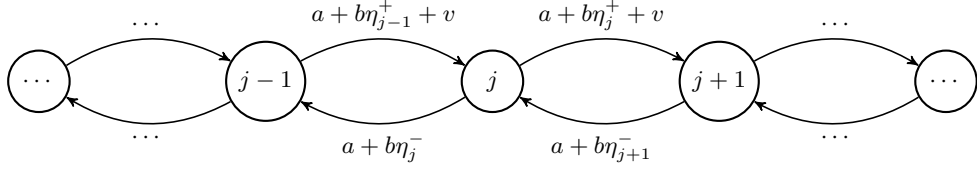


FIG. 2. Transitions between states that lead to the ODE system (2.1). The fractions  $\eta_j^\pm$  are defined in (2.2).

Note that the coefficient of  $u_{xx}$  changes sign at the critical velocity

$$v_c := bd - 2a. \quad (2.4)$$

The uniform steady state is stable provided that  $v > v_c$ . In the opposite case when  $0 \leq v < v_c$  (or equivalently,  $bd > 2a + v$ ), the diffusion coefficient is negative and so diffusion equation (2.3) ill-posed (unstable). In this case, higher order terms (up to fourth order) in the expansion are needed to capture the aggregation behaviour. After performing this expansion following the procedure in [5], we obtain a PDE approximation

$$u_t = -Au_{xx}(x, t) - Bu_{xxxx} + C \left( \frac{u_x u_{xx}}{u} \right)_x - vhu_x(x, t) - v \frac{h^3}{6} u_{xxx}, \quad (2.5)$$

where

$$A = \frac{h^2}{2}(bd - 2a - v), \quad B = \frac{h^4}{24}(b(d^3 + 2d^2 + 3d + 1) - 2a - v), \quad \text{and } C = \frac{h^4}{24}b(2d + 1)(d + 1)^2. \quad (2.6)$$

Equation (2.5) reduces to the model from [5] when  $v = 0$ . Note that  $B > 0$  automatically whenever  $A > 0$ , since  $b(d^3 + 2d^2 + 3d + 1) - 2a - v > bd - 2a - v > 0$ . This fourth-order term effectively stabilizes the high-frequency modes and makes the equation well-posed.

Following [5], we non-dimensionalize (2.5) to make the coefficients of  $u_{xx}$  and  $u_{xxxx}$  be unity. Namely, we scale space and time as

$$x = \sqrt{B/A}\tilde{x}, \quad t = \frac{B}{A^2}\tilde{t}. \quad (2.7)$$

Dropping the tilde, we obtain the dimensionless PDE

$$u_{\tilde{t}} = -u_{xx} - u_{xxxx} + \alpha \left( \frac{u_x u_{xx}}{u} \right)_x - \beta u_x - \gamma u_{xxx}, \quad (2.8)$$

where

$$\begin{aligned} \alpha &= \frac{b(2d + 1)(d + 1)^2}{(b(d^3 + 2d^2 + 3d + 1) - 2a - v)}, \\ \beta &= 3^{-1/2}v \left( \frac{b(d^3 + 2d^2 + 3d + 1) - 2a - v}{(bd - 2a - v)^3} \right)^{1/2}, \\ \gamma &= \frac{2}{\sqrt{3}}v \frac{1}{\sqrt{(b(d^3 + 2d^2 + 3d + 1) - 2a - v)(bd - 2a - v)}}. \end{aligned} \quad (2.9)$$

Equation (2.8) generalizes the model derived in [5], as it contains additional terms  $-\beta u_x - \gamma u_{xxx}$  which induce a pulse motion. We now generalize the method outlined in [5] to derive an exact solution of (2.8) moving at a constant speed  $\tilde{c}$  to be determined. We start with a travelling pulse ansatz of the form  $u = u(x - \tilde{c}t)$ . Then (2.8) reduces to an ODE

$$-\tilde{c}u_y = -u_{yy} - u_{yyyy} + \alpha \left( \frac{u_y u_{yy}}{u} \right)_y - \beta u_y - \gamma u_{yyy}; \quad y = x - \tilde{c}t.$$

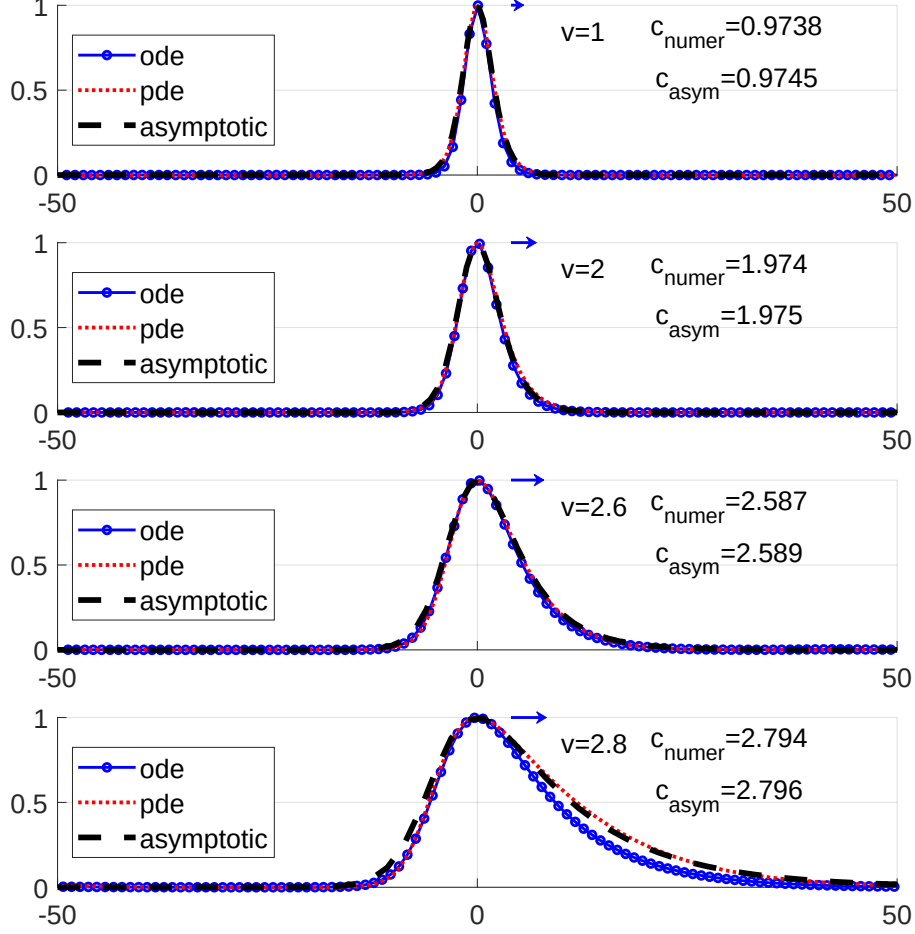


FIG. 3. Model I: Comparison between the discrete ODE model (2.1), the PDE approximation (2.8) and the asymptotic solution (2.17). For the ODE model the parameters were taken to be:  $a = 1$ ,  $b = 5$ ,  $N = 100$  bins on the domain of size  $L = 100$  so that  $h = 1$ , and  $v$  as indicated; For the PDE model, we used implicit-explicit Euler scheme (implicit on diffusion and biharmonic terms, explicit on all other terms) with  $n = 150$  meshpoints on the domain of size  $[0, 100]$ . All profiles are recentered on the pulse maximum, and the height is normalized to unity (since the equations are invariant under scaling of  $u$ , scaling it does not change the speed or profile). Periodic boundary conditions were used for both ODE and PDE models. For each frame,  $c_{\text{numer}}$  is the speed of the pulse propagation, computed from the direct numerical simulations of the ODE by tracking pulse location, whereas  $c_{\text{asym}}$  is the asymptotic prediction as given by the formula (2.19).

Integrate once and assume  $u$  decays at  $\infty$ . We obtain

$$u''' = (-\beta + \tilde{c})u - u' - \gamma u'' + \alpha \frac{u''u'}{u}.$$

Because of the scaling symmetry  $u \rightarrow \lambda u$ , we get a reduction of order using the transformation

$$u = \exp(v); \quad v' = z$$

to obtain

$$z'' = -z + (\alpha - 3)zz' + (\alpha - 1)z^3 - \beta + \tilde{c} - \gamma(z^2 + z'), \quad z = u_y/u.$$

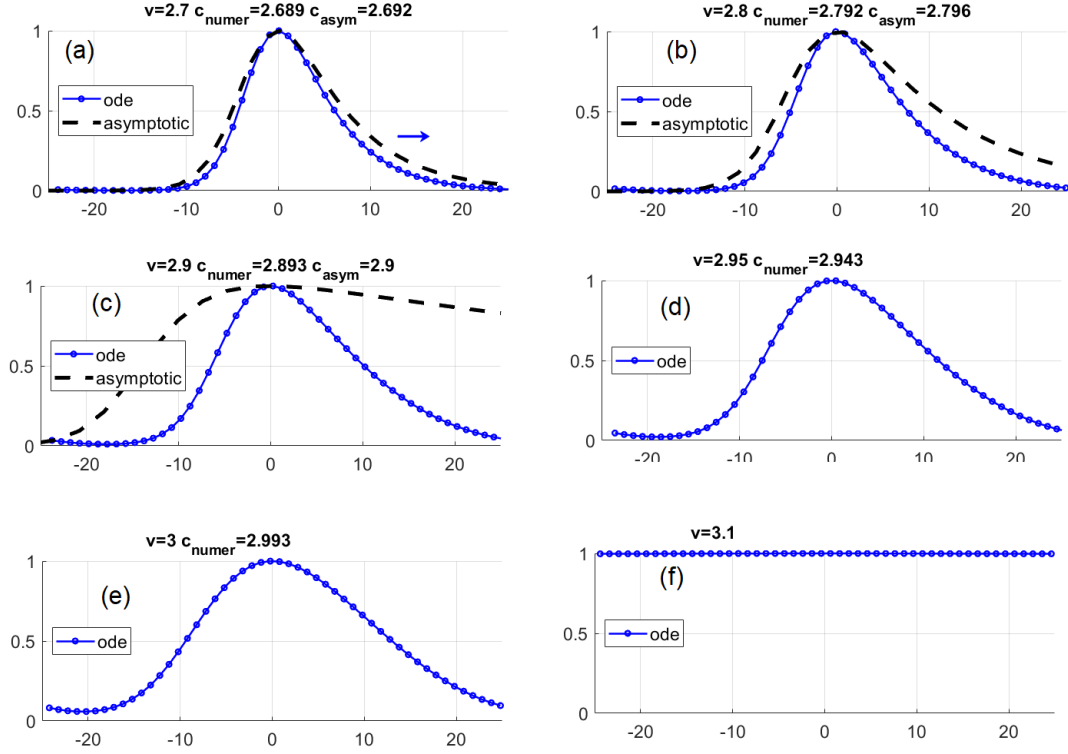


FIG. 4. Model I: Transition from a localized cluster (when  $v < v_*$ ) to a more broad non-homogeneous state when  $v_* < v < v_c$  and finally to a homogeneous constant state for  $v > v_c$ . Here,  $a = h = d = 1$ ,  $b = 5$  and  $v$  is as indicated. All profiles have been rescaled to have a height of unity, and shifted to have the peak at the origin. Blue line (“ode”) is the numerical solution to (2.1), at time  $t = 10000$ . Black dashed line is the asymptotic solution (2.17), where relevant. For these parameter values,  $v_* = 2.9099$  (given by (2.22)) and  $v_c = 3$ . In (a)-(c),  $v < v_*$  and the localized cluster of the form (2.17) exists, although the approximation breaks down as  $v \rightarrow v_*^-$ . In (d)-(e), the localized state breaks down completely, and the breadth of the cluster is comparable to the domain size. In (f), the solution eventually converges to a homogeneous steady state.

We rewrite this as a system of ODEs,

$$\frac{dz}{dy} = w; \quad (2.10)$$

$$\frac{dw}{dy} = -z + (\alpha - 3)zw + (\alpha - 1)z^3 - \beta + \tilde{c} - \gamma(z^2 + w). \quad (2.11)$$

We obtain a 1st order Abel ODE of the form

$$\frac{dw}{dz} = \frac{-z}{w} + (\alpha - 3)z + (\alpha - 1)\frac{z^3}{w} + \frac{-\beta + \tilde{c}}{w} - \gamma\left(\frac{z^2}{w} + 1\right). \quad (2.12)$$

Next we use the ansatz

$$w = A_2 z^2 + A_1 z + A_0. \quad (2.13)$$

This ansatz is self consistent if and only if

$$\begin{aligned} A_2 &= \frac{\alpha - 1}{2}, \quad A_1 = -\frac{(\alpha + 1)\gamma}{\alpha + 3}, \quad A_0 = -\frac{1}{2} + \frac{(\alpha + 1)\gamma^2}{(\alpha + 3)^2}, \\ \tilde{c} &= \beta - \frac{\gamma}{\alpha + 3} + \frac{2(\alpha + 1)\gamma^3}{(\alpha + 3)^3}. \end{aligned} \quad (2.14)$$

Equation (2.14) gives the travelling speed. To obtain the pulse profile, we unwind the transformations. Write

$$\frac{dz}{dy} = A_2 z^2 + A_1 z + A_0 = c_1 \left( (z + c_2)^2 - c_3^2 \right), \quad (2.15)$$

where

$$c_1 = A_2, \quad c_2 = \frac{A_1}{2A_2}, \quad c_3 = \sqrt{\frac{A_1^2}{4A_2^2} - \frac{A_0}{A_2}}. \quad (2.16)$$

Integrating (2.15) then yields

$$z = -c_2 - c_3 \tanh(c_1 c_3 y),$$

so that  $u = \exp(\int z)$ , and hence

$$u = C \exp(-c_2 y) (\operatorname{sech}(y c_1 c_3))^{1/c_1}. \quad (2.17)$$

The constant  $C$  is fixed by the total mass, as set by initial conditions.

When  $v = 0$ , we find  $c_2 = 0$ ,  $\tilde{c} = 0$ , and (2.17) reduces to the stationary symmetric sech profile as derived in [5].

Going back to the original variables  $(x, t)$  in (2.7), the original speed  $c$  is related to  $\tilde{c}$  via

$$c = \tilde{c} A^{3/2} B^{-1/2} \quad (2.18)$$

and the moving cluster profile is given by (2.17) with  $y = \sqrt{A/B}(x - ct)$ . In the special case  $a = 1, d = 1, h = 1$  we have

$$c = \frac{-43v^4 + (1735b - 194)v^3 - 27(73b - 6)(11b - 2)v^2 + 27(11b - 2)^2(31b - 2)v}{81(11b - 2 - v)^3} \quad (2.19)$$

To validate formula (2.19), take  $a = 1, b = 5, d = 1, h = 1$ . In this case, the cluster forms (i.e. the uniform equilibrium is unstable) provided that  $0 \leq v < 3$  (refer to (2.4)). Figure 3 shows a comparison between the asymptotics, the original ODE model (2.1) as well as the PDE approximation (2.8) for several values of  $v$  in that range. Note that the cluster becomes more asymmetric and wider as  $v \rightarrow 3^-$ . For  $v \geq 3$ , the solution converges to a uniform density, as predicted, even starting with a cluster-type initial condition. Finally, we observe the excellent predictive power of the formula (2.19) for cluster speed  $c$  (denoted by  $c_{\text{asym}}$  in the figures); it accurately recovers the actual observed speed in the ODE simulations (denoted by  $c_{\text{numer}}$  in the figures) across the entire range of  $v$ .

It is rather intriguing that the speed  $c$  given by (2.19) is very close not only to the numerically computed value, but also to  $v$  itself. In other words, the cluster as a whole moves with a speed that is very close to the individual particle speed. In fact, the biggest relative difference between  $c$  and  $v$  occurs for small values of  $v$ , in which case (2.19) reduces to

$$c = \frac{31b - 2}{33b - 6} v + O(v^2). \quad (2.20)$$

With  $b = 5$  as above, the biggest deviation is  $153/159$ , or 3.8%.

Note that for  $y \rightarrow +\infty$ , we have  $u \sim C \exp(-(c_2 + c_3)y)$ , whereas for  $y \rightarrow -\infty$ ,  $u \sim C \exp(-(-c_2 + c_3)(-y))$ . It follows that  $u$  decays at  $\pm\infty$  if and only if  $c_3 > |c_2|$ . This happens if and only if  $A_0/A_2 < 0$ . Since  $A_2 > 0$ , this is equivalent to  $A_0 < 0$  or

$$(\alpha + 3)^2 > 2(\alpha + 1)\gamma^2. \quad (2.21)$$

When  $a, d, h = 1$ , condition (2.21) is equivalent to  $v < v_*$ , where  $v_*$  satisfies

$$19v_*^3 + (-469b + 146)v_*^2 + 27(11b - 2)(13b - 6)v_* - 27(b - 2)(11b - 2)^2 = 0. \quad (2.22)$$

For example when  $b = 5$ , we obtain  $v_* = 2.9099$ , whereas the threshold for linear stability of a constant state is  $v_c = 3 > v_*$ . Consequently, a localized travelling pulse (which decays to zero as  $y \rightarrow \pm\infty$ ) exists only for  $0 < v < v_* < v_c$ . When  $v > v_c$ , the constant state is stable. In the narrow regime  $v_* < v < v_c$ , the constant state is unstable but the fully localized solution of the form (2.17) also does not exist. Instead, in that narrow band we observe non-constant travelling states which do not decay exponentially to zero. This is illustrated in Figure 4. More generally, Figure 6(a) shows the overall bifurcation diagram of  $b$  vs.  $v$ . It appears that the narrow band  $v_* < v_c$  (labelled “gap” in the figure) exists for all  $v_c > 0$  (and indeed, from (2.22),  $v_* = v_c = 0$  when  $b = 2$ ).

### 3. MODEL II: BIASED AGGREGATION.

Instead of introducing an extra term for directed motion in (2.1), an alternative is to incorporate direction bias directly into the aggregation rate. Suppose that rather than choosing a neighbour at random, the cell prefers to choose the neighbours to the right (for example due to light gradient “illuminating” the right side more than the left side, or because the cells are initially polarized towards the right). To simplify the computations, we will assume the sensing radius  $d$  to be  $d = 1$ . We then modify the model (2.1) as follows:

$$\frac{dU_j}{dt} = a(U_{j-1} - 2U_j + U_{j+1}) + b(\eta_{j+1}^- U_{j+1} - U_j + \eta_{j-1}^+ U_{j-1}); \quad (3.23)$$

$$\eta_j^+ = \frac{(1 + hr)U_{j+1}}{(1 + hr)U_{j+1} + (1 - hr)U_{j-1}}, \quad \eta_j^- = \frac{(1 - hr)U_{j-1}}{(1 + hr)U_{j+1} + (1 - hr)U_{j-1}}. \quad (3.24)$$

The new parameter  $r$  represents the bias towards choosing a neighbour to the right, and  $h = L/n$  is the bin width (assumed to be small). Note that  $\eta_j^+ + \eta_j^- = 1$  still holds. As before, we expand to fourth order in grid spacing  $h$ , obtaining the PDE

$$u_t = \left[ au_{xx} + b \left( -\frac{u_{xx}}{2} - ru_x \right) \right] h^2 + \left[ a \frac{u_{xxxx}}{12} + b \left\{ \left( -\frac{7u_{xxx}}{24} + \frac{u_{xx}u_x}{2u} \right) + \left( -\frac{u_{xx}}{6} + \frac{u_x^2}{u} \right) r + u_{xx}r^2 \right\} \right] h^4 \quad (3.25)$$

Although more complex than the PDE (2.8), the analysis follows along similar lines. In particular, linear analysis shows that the homogeneous state is unstable provided that

$$a + b \left( -\frac{1}{2} + h^2 r^2 \right) < 0. \quad (3.26)$$

By analogy with Model I, we define the critical value  $r_c$  to be the root of (3.26):

$$r_c = \frac{1}{h} (1/2 - a/b)^{1/2}. \quad (3.27)$$

The homogeneous state is unstable when  $|r| < r_c$ , and numerics indicate that clusters form when this instability is triggered.

Following §2, we seek a travelling cluster solution of the form

$$u(x, t) = u(y), \quad y = x - ct,$$

corresponding to a cluster travelling to the right with a constant speed  $c$ . The procedure is then the same as in §2. Upon integrating once, we obtain a 3rd order ODE

$$0 = \left( au_y + \left( -ru - \frac{u_y}{2} \right) b \right) h^2 + \left[ a \frac{u_{yyy}}{12} + b \left\{ \left( -\frac{7u_{yyy}}{24} + \frac{u_{yy}u_y}{2u} \right) + \left( -\frac{u_{yy}}{6} + \frac{u_y^2}{u} \right) r + u_y r^2 \right\} \right] h^4 + cu \quad (3.28)$$

Substitute  $u = e^v$ ;  $v' = z$ ,  $\frac{dz}{dy} = w$ ,  $\frac{dw}{dy} = \frac{dw}{dz}w$ , to obtain a first order ODE

$$0 = h^4 w (2a - 7b) \frac{dw}{dz} + h^4 (2a + 5b) z^3 + 20b h^4 r z^2 + 3h^4 (2a - 3b) wz + 12h^2 (2b h^2 r^2 + 2a - b) z - 4b h^4 r w - 24b h^2 r + 24c.$$

We now substitute  $w = A_2 z^2 + A_1 z + A_0$ , to obtain a polynomial system relating  $A_0, A_1, A_2$  and  $c$ . It is fully solvable, having two solutions. One, corresponding to  $A_2 = -1$ , is non-physical, while the other has

$$A_0 = \frac{4b(108a^2 - 572ab + 1447b^2)r^2}{9(7b - 2a)(2a - 11b)^2} + \frac{6(2a - b)}{(7b - 2a)h^2}, \quad (3.29)$$

$$A_1 = \frac{4b(22a - 65b)r}{3(7b - 2a)(2a - 11b)}, \quad A_2 = \frac{2a + 5b}{2(7b - 2a)}, \quad (3.30)$$

$$c = -\frac{28b^2 h^4 (108a^2 - 572ab + 1447b^2)r^3}{81(2a - 11b)^3} - \frac{h^2 b(22a + 19b)r}{3(2a - 11b)}. \quad (3.31)$$

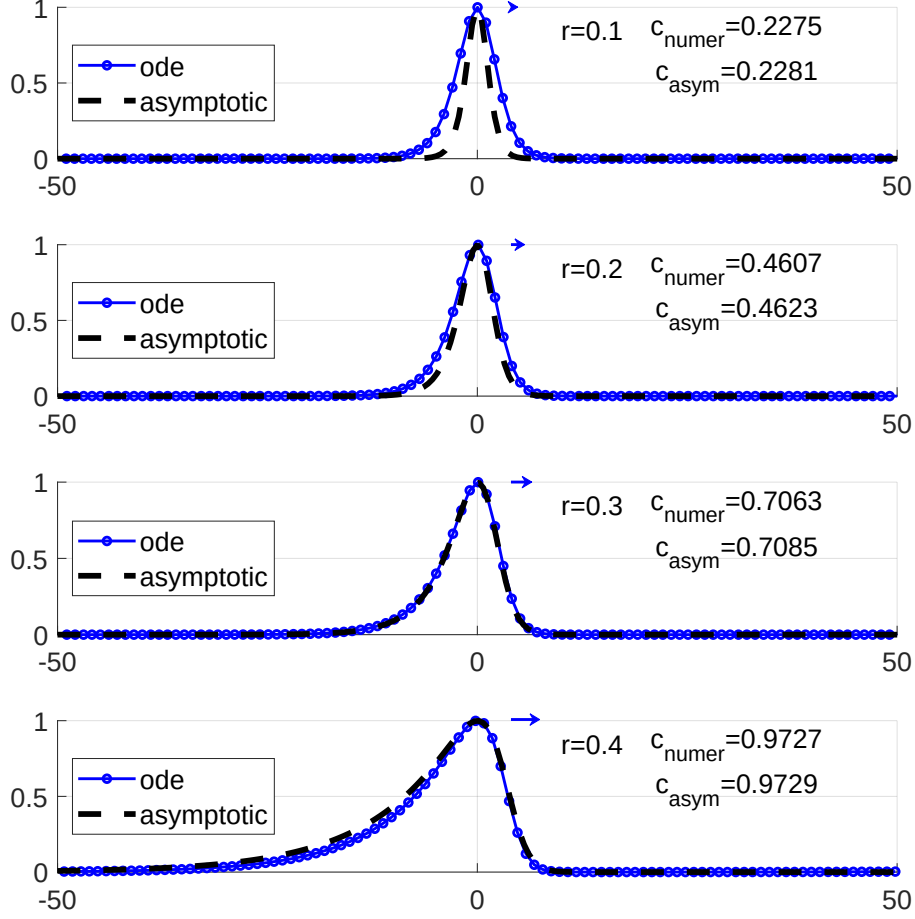


FIG. 5. Model II: Comparison between the discrete ODE model (3.23) and the asymptotic solution (3.29-3.31, 2.16, 2.17). For the ODE model, the parameters were taken to be:  $a = 1$ ,  $b = 2.5$ ,  $N = 100$ ,  $L = 100$ ,  $h = 1$ , with periodic boundary conditions and  $r$  as indicated. For each frame,  $c_{\text{numer}}$  is the speed of the pulse propagation, computed from the direct numerical simulations by tracking pulse location, whereas  $c_{\text{asym}}$  is the asymptotic prediction as given by the formula (3.31). The last frame ( $r = 0.4$ ) corresponds to a bistable region (see also Figure 6).

This determines the speed  $c$ , as well as the corresponding cluster profile given by (2.16, 2.17). Figure 5 shows a direct comparison between numerical simulations of the ODE model (3.23) and the asymptotic profile as well as group velocity (3.31). Excellent agreement is observed.

As in Model I, a localized cluster ceases to exist when  $A_0 = 0$ , corresponding to the value of  $r = r_*$  given by

$$r_* = \frac{1}{h} \sqrt{\frac{27(b-2a)(2a-11b)^2}{2b(108a^2 - 572ab + 1447b^2)}}. \quad (3.32)$$

(The cluster exists when  $|r| < r_*$  and does not exist when  $|r| > r_*$ ). In the example from Figure 5 where  $a = 1$ ,  $b = 2.5$ ,  $h = 1$ , we obtain  $r_* = 0.4768$  and  $r_c = 0.3162$ , so that  $r_* > r_c$ . We have the following situation: when  $r < r_c$ , the homogeneous state is unstable and localized cluster exists. When  $r > r_*$ , the homogeneous state is stable and cluster does not exist. When  $r_c < r < r_*$ , the cluster exists and the homogeneous state is stable. Numerics further indicate that the cluster is indeed stable in this band once formed, see the frame for  $r = 0.4$  in Figure 5. As such,  $r \in (r_c, r_*)$  is a region of bistability where both cluster and homogeneous state can be observed depending on the initial conditions. Figure 6(a) shows the overall bifurcation diagram of  $b$  vs.  $r$ ; the bistability band  $r_c < r_*$  exists for all  $b > 2a$ .

#### 4. DISCUSSION

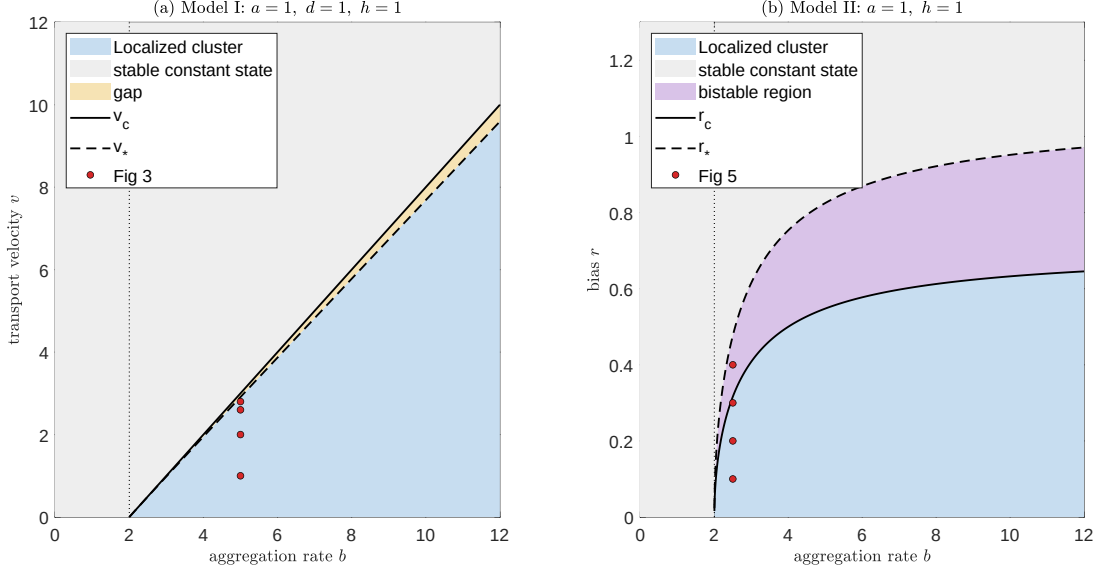


FIG. 6. (a) Bifurcation diagram for Model I, in the  $(b, v)$  plane, with  $a = h = d = 1$ . Constant steady state is stable in the grey region  $v > v_c$ . Localized solutions exist in the blue region  $v < v_*$ . Since  $v_* < v_c$ , there is a “gap” region where the constant state is unstable but fully localized clusters do not exist (see also Figure 4). Red dots denote the simulation parameters from Figure 3. (b) Bifurcation diagram for Model II, in the  $(b, r)$  plane with  $a = h = d = 1$ . Constant steady state is stable in the grey region  $r > r_c$ . Localized solutions exist in the blue region  $r < r_*$ . Since  $r_* > r_c$ , there is a bistable region where constant stable state coexists with a localized cluster state. Red dots denote the simulation parameters from Figure 5.

We have generalized as well as simplified the model proposed in [1, 5] to incorporate directed motion of cells. We proposed two models that induce group motion, either by adding simple directed motion of cells (Model I), or by adding a biased sensing mechanism (Model II). In the limit of a large number of particles, we derived an analytical expression for both the aggregation profile as well as its group velocity. This generalizes results in [5], where the model leads to a stationary spike (zero velocity). The advantage of these models is the relative simplicity of the aggregation mechanism, and availability of the full analytical description of the cluster profile as well as its velocity in the mean-field limit. This is one of the very few models where such exact and full description is possible.

Let us contrast the two models. In Model I, each cell is assigned an intrinsic velocity  $v$ . We found that although the overall group velocity of the cluster  $c$  was definitely not equal to individual cell velocity  $v$ , it was surprisingly close (within 4% or less for all the cases we studied, see e.g. (2.20)). By contrast, Model II does not dictate intrinsic particle velocity, and instead assigns a bias  $r$ , so that it “weights” its neighbours to the right more than its neighbours to the left. The overall group velocity is a nonlinear (cubic) function of the bias  $r$  that we explicitly computed in (3.31).

Another distinction is the profile of the right-moving cluster shown in Figures 3, 5. The cluster in Model I is steeper on the left and shallower on the right. The opposite is true for Model II. Such asymmetry is present in many models of cluster motion, but usually the cluster is sharper on the right (in the direction of motion, as in Model II). This is the case, for instance, in the Klausmeier model [27], as well as in many cellular aggregation models [4]. This suggests that Model II may be more relevant for travelling biological clusters.

An interesting new phenomenon is the existence of a “gap” window in Model I (where neither uniform state is stable, nor the localized cluster exists), and bistability window in Model II (where both the uniform state is stable and localized cluster exists) – see Figure 6. Both of these phenomena are specific to moving pulses: no such windows exist in the original model [5]. Within the narrow “gap” window, numerics show a novel type of solutions which are neither localized, nor uniform, but span the entire domain (Figure 4). Further insights into this region is an interesting open question.

Our results have several physical implications. First, in Model I, we found that decreasing the aggregation strength, or increasing the fluid flow past some critical threshold  $v_c$  flattens out the cluster, and eventually disables aggregate cohesion. This is consistent with experimental observations that microfluidic flow strength can toggle between modes of cell behaviour (such as amoeboid vs mesenchymal [28]) or, in our model, single vs collective motion. As far as

cell types, larger random motility or lower sensing radius in the cells lowers the critical flow velocity for transition, making aggregates less stable. Hence, to form stable aggregates, the cells should have stronger cell-cell attraction, sense neighbours over a larger distance, and reduce their random exploration. In contrast, in Model II, we found that increasing the cells' biased motion (e.g., faster polarized cells) makes the cluster less symmetric, with a longer shallower "tail". Eventually, straggler cells are lost from the back so that the cluster cannot be maintained. In other words, if cells tend to move too rapidly in a biased direction, neighbours behind them cannot keep up. This model helps to understand the behaviour of "cell trains" moving along 1D adhesive strips, as in [11], where a transition from single cells to a band of cells can be observed.

## 5. ACKNOWLEDGEMENTS

Claude AI was shown an early draft of this paper. It discovered and sketched the "gap" and "bistable" regions in Figure 6. The authors independently verified the correctness of the figure.

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