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## *A Survey of the Literature on Agents Navigating in Constrained Environments*

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### References

- [1] J. P. Agnelli, B. Buffa, D. Knopoff, and G. Torres, “A Spatial Kinetic Model of Crowd Evacuation Dynamics with Infectious Disease Contagion,” *Bulletin of Mathematical Biology*, vol. 85, no. 4, p. 23, February 2023.
- [2] M. Beermann and A. Sieben, “The connection between stress, density, and speed in crowds,” *Scientific Reports*, vol. 13, no. 1, August 2023.
- [3] N. Bellomo, J. Liao, A. Quaini, L. Russo, and C. Siettos, “Human behavioral crowds review, critical analysis and research perspectives,” *Mathematical Models and Methods in Applied Sciences*, vol. 33, no. 08, pp. 1611–1659, July 2023.
- [4] A. Buttenschön and L. Edelstein-Keshet, “Bridging from single to collective cell migration: A review of models and links to experiments,” *PLOS Computational Biology*, vol. 16, no. 12, December 2020.
- [5] A. Buttenschön, S. Sinclair, and L. Edelstein-Keshet, “How Cells Stay Together: A Mechanism for Maintenance of a Robust Cluster Explored by Local and Non-local Continuum Models,” *Bulletin of Mathematical Biology*, vol. 86, no. 11, p. 129, September 2024.

**Biological context:** Migrating cell clusters occur in development and disease, e.g. collective cell movement in Dictyostelium slugs and in the zebrafish lateral-line organ, as well as metastatic tumor cell clusters. These examples motivate a model of cells that interact via secreted cues (attractant/repellent) to maintain a compact group.

**Model:** A 1D continuum PDE for cell density  $\rho(x, t)$  with pure attraction–repulsion (no random motility) is used. Cells experience a velocity proportional to  $-\nabla(K * \rho)$  (velocity proportional to Force due to negligible cellular inertia), where the convolution  $(K * \rho)(x) = \int_{\mathbb{R}} K(x - y)\rho(y) dy$  sums all distance-dependent interactions. The kernel is a symmetric Morse-type potential  $K(x) = Rr \exp(-|x|/r) - Aa \exp(-|x|/a)$ , encoding short-range repulsion (strength  $R$ , range  $r$ ) and longer-range attraction (strength  $A$ , range  $a$ ). Analysis focuses on steady states (cluster profiles) with zero-flux boundary conditions (“zero contact angle”) (no migration is modeled).

**Clustering analysis:** The paper investigates when and how non-uniform steady clusters form. Key findings include:

- **Stability criterion:** Linear stability shows that stable clusters exist when  $\frac{R}{A} > 1$ ,  $\frac{a}{r} > 1$ ,  $\frac{R}{A} < \frac{a^2}{r^2}$ . That is, repulsion strength is greater than attraction strength while attraction range greater than repulsion range.
- **Influence of parameters:** Increasing attraction strength  $A$  or its range  $a$  enlarges and stabilizes clusters, while increasing repulsion  $R$  or range  $r$  shrinks or disperses them. If attraction is too weak (small  $A$  or  $a$ ), no cluster forms; if repulsion is too strong, the cluster cannot hold together.

**Conclusions:** A balance of short-range repulsion and longer-range attraction (captured by the Morse potential) can maintain a robust 1D cell cluster. Tuning the amplitudes  $R, A$  and length-scales  $r, a$  controls the cluster outcome: stronger or longer-ranged attraction supports larger, more stable clusters, while excess repulsion prevents clustering.

- [6] B. A. Camley and W.-J. Rappel, “Physical models of collective cell motility: From cell to tissue,” *Journal of Physics D: Applied Physics*, vol. 50, no. 113002, February 2017.

This paper surveys agent-based models that resolve individual cells to study collective motility in constrained and unconstrained environments.

#### Four key ingredients of collective motility:

- *Single-cell motility:* characteristic speed and orientation distributions.
- *Cell shape & mechanics:* representation of cell–cell adhesion, repulsion, and deformation.
- *Polarity mechanisms:* rules by which cells choose their direction of motion.
- *Biochemical signalling:* intercellular exchange of attractants, repellents, and other cues.

#### Single-cell motility statistics:

- Velocity distributions: Gaussian (zero mean), polarized (nonzero mean), or intermittent (switching between low/high states).
- Persistence time: characteristic timescale over which velocity correlations decay.
- Low–Reynolds-number limit: overdamped force balance  $F - \gamma v = 0$ , with drag coefficient  $\gamma$  and active force  $F$  aligned with polarity  $\mathbf{p}$ .
- Polarity dynamics:  $\partial_t \mathbf{x}_{\text{cell}} = \mathbf{v}_{\text{cell}} = \mathbf{p}$ ,  $\partial_t \mathbf{p}(t) = -\frac{\partial W}{\partial \mathbf{p}} + \int_{-\infty}^t dt' K(t - t') \mathbf{p}(t') + \sigma \xi(t)$ , where  $W(\mathbf{p})$  is a polarity potential,  $K(t)$  a memory kernel, and  $\langle \xi_i(t) \xi_j(t') \rangle = \delta_{ij} \delta(t - t')$ .

#### Cell shape & mechanical interaction models:

- *Isotropic deformable particles:* Overdamped force-balance with pairwise potentials combining short-range repulsion (no overlap) and longer-range adhesion. Minimal but may misrepresent tissue mechanics near jamming.
- *Voronoi/vertex models:* Cells as polygons (vertices) or Voronoi regions around cell centers. Interface energies via Hamiltonians penalizing deviations from preferred area/perimeter; active forces added. Best for confluent layers; cannot represent free cell edges naturally.
- *Subcellular element models:* Cells as networks of elements (particles + springs). Capture intra-cellular mechanics and front/back polarity by differential bond dynamics. Useful for rheology studies but computationally heavier.

- *Cellular Potts models*: Lattice spins label cells; energy  $H = \sum_{a,b} J_{ab}(1 - \delta_{\sigma(a),\sigma(b)}) + \sum_i \lambda(A_i - A_{i,0})^2$ , evolved by Monte Carlo updates (Metropolis rule). Efficient for many cells; time and forces are emergent and less physically explicit.
- *Phase-field models*: Each cell has a smooth indicator field  $\phi(\mathbf{r}) \in [0, 1]$ . Dynamics by variational derivative of a Hamiltonian:  $\partial_t \phi + \mathbf{v}_{\text{active}} \cdot \nabla \phi = -\frac{1}{\zeta \epsilon} \frac{\delta H}{\delta \phi}$ , where  $\zeta$  is friction,  $\epsilon$  interface width. Can couple shape, mechanics, and biochemistry; best for  $< 100$  cells due to PDE cost.

**Recommendations** Choose model complexity to match the biological question: for large-scale collective patterns, isotropic or Potts models suffice; for detailed shape–motility couplings or mechanochemical feedback, phase-field or subcellular element models are preferred.

- [7] I. Hecht, H. Levine, W.-J. Rappel, and E. Ben-Jacob, ““Self-Assisted” Amoeboid Navigation in Complex Environments,” *PLOS ONE*, vol. 6, no. 8, August 2011.

**Stochastic Compass Model in Simple Environments** The authors present a simulation-based model of amoeboid chemotaxis in both open space and mazes. Cells extend pseudopods in directions biased by the gradient direction plus noise, with noise (Gaussian width) inversely proportional to gradient steepness. The closest membrane point to the internal gradient vector is selected as the new front, which is then extended and later retracted. Cell shape is governed by cortical tension, area conservation, and friction.

#### Obstacle Navigation and Cell Shape

- Protrusions are blocked at obstacle boundaries, forcing cells to extend around them.
- Model can be tuned for single or multiple protrusions to simulate different cell types.
- Navigation is effective only when obstacles are small or comparable to cell size.

#### Maze Performance with Simple Gradient

- Maze walls were porous to chemoattractant; thus, consistent gradient formed throughout, regardless of maze structure.
- Perpendicular walls posed major barriers, causing cell trapping or slow movement.
- Low noise enabled faster but riskier movement; high noise increased exploration but reduced efficiency.
- Variable noise (apparently seen in *Dictyostelium*) showed improved adaptability.
- Overall, gradient-only strategy had low success rates and was maze-structure dependent.

#### Self-Generated Chemorepulsion

- Cells secreted a repulsive chemical to avoid previously explored regions.
- The repellent acted as a diffusing memory, steering cells away from traps.
- This strategy significantly boosted success rates (0% to 70%) and search efficiency.

#### Applications and Limitations

- Relevant for cell navigation in porous extracellular matrix (ECM).

- Paper is purely computational; some parameters were based on prior experiments.
- Mazes were arbitrarily designed, though authors note small changes could drastically alter difficulty. It seems likely that small tweaks could be made to maze structure to significantly reduce success rates.

### Methods:

The cell is modeled as a chain of connected nodes that respond to internal and external forces. The direction of motion is guided by an internal compass  $\text{int}$  determined by the external gradient  $\text{ext}$  plus noise:  $\text{int} = \text{ext} + \eta$  where  $\eta$  is Gaussian noise with zero mean and variance inversely proportional to the chemoattractant gradient steepness. The total force acting on each node is:  $F_{\text{total}} = F_{\text{protrusion}} + F_{\text{tension}} + F_{\text{pressure}} + F_{\text{drag}}$ . Each component of the force is defined as:

- $F_{\text{protrusion}}$ : Protrusive force proportional to local activation, centered on a patch aligned with the internal compass.
- $F_{\text{tension}}$ : Cortical tension based on curvature  $\kappa$ , membrane rigidity  $\lambda$ , and spontaneous curvature  $\kappa_0$ .
- $F_{\text{pressure}}$ : Restores cell area  $A$  to a constant, acting as an effective pressure.
- $F_{\text{drag}}$ : Damping force proportional to local velocity  $v$ , imposing speed limits.

The node motion is then given by:  $\frac{dr}{dt} = v = \frac{F_{\text{total}}}{\gamma}$  where  $\gamma$  is the drag coefficient.

- [8] S. Jain, V. M. L. Cachoux, G. H. N. S. Narayana, S. de Beco, J. D’Alessandro, V. Cellerin, T. Chen, M. L. Heuzé, P. Marcq, R.-M. Mège, A. J. Kabla, C. T. Lim, and B. Ladoux, “The role of single-cell mechanical behaviour and polarity in driving collective cell migration,” *Nature Physics*, vol. 16, no. 7, pp. 802–809, July 2020.

### Collective Cell Migration in Ring Geometry:

This study explores how epithelial cells migrate collectively in annular (ring-shaped) domains. While single-cell migration is well studied, collective migration introduces complex behaviors, including leading cells, follower cohorts, and bulk movement.

#### Coordination Dynamics:

- Coordination was quantified using the average cross product of each cell’s unit velocity vector and its radial position vector (values: +1 = clockwise, -1 = anti-clockwise, 0 = unaligned).
- Cells began with oscillatory motion, but coordination peaked as cell trains collided and merged.
- Ultimately, cells reached confluence and adopted a stable coordinated direction (either +1 or -1).
- Coordination degraded with proliferation due to crowding (“cell jamming”), but was preserved when cell division was limited.

#### Train Collisions and Polarity Reversal:

- Colliding cell trains triggered directional reversal in one train via contact inhibition of locomotion.
- Reversal was linked to rapid polarity switching in the colliding cells.
- Final direction was best predicted by the size and speed of the last train to collide.
- Lamellipodial protrusions in leader cells were key: dominant leaders induced polarity reversal in opposing cells.

### Single-Cell Dynamics and Emergent Coordination:

- Cells formed unidirectional polarity gradients within the group.
- Follower cells developed "cryptic lamellipodia" that tucked under leading cells, enabling persistent, coordinated movement.
- Disrupting lamellipodia in a few cells halted global coordination.
- Cell-cell junctions were required for initiating, but not maintaining, collective motion.
- Once coordination emerged, it persisted even after physically disrupting the train or isolating cells.

### Simulation and Implications:

- A simple ring-domain simulation incorporating cell polarity and adhesion reproduced experimental findings.
- Long-term memory of polarity emerged as a critical mechanism, decoupling sustained motion from ongoing adhesion.
- Highlights how single-cell dynamics shape global migration—relevant for development, wound healing, and metastasis.

- [9] D. Kaziyeve, P. Stutz, G. Wallentin, and M. Loidl, "Large-scale agent-based simulation model of pedestrian traffic flows," *Computers, Environment and Urban Systems*, vol. 105, October 2023.
- [10] B. Libberton, M. Binz, H. van Zalinge, and D. V. Nicolau, "Efficiency of the flagellar propulsion of *Escherichia coli* in confined microfluidic geometries," *Physical Review E*, vol. 99, no. 1, January 2019.

### Effects of Channel Width on *E. coli* Motility

- *E. coli* exhibits preferential swimming near boundaries, particularly along edges formed by intersecting walls. This edge-following behavior enhances directed movement under confinement.
- Movement speed increased when entering the channels, and peaked around the 4  $\mu\text{m}$  width. This is assumed to be due to the reduced dissipation of exerted mechanical force because of wall proximity. Smaller channel sizes might interrupt flagellar rotation.

### Characteristics of Bacterial Motion

- *E. coli* uses run-and-tumble locomotion, alternating between straight runs and stochastic reorientation events. Confined environments modify these trajectories through surface interactions.
- Hydrodynamic interactions with boundaries cause alignment of the cell body and flagella with surfaces, enhancing surface accumulation.
- The propulsion efficiency is found to be geometry-dependent, with increased energy transfer to fluid motion near boundaries compared to unconfined settings.

- [11] F. Martinez-Gil, M. Lozano, and F. Fernández, "Emergent behaviors and scalability for multi-agent reinforcement learning-based pedestrian models," *Simulation Modelling Practice and Theory*, vol. 74, pp. 117–133, May 2017.

Somewhat recent and relatively well cited paper that cited Schweitzer's book. Not sure exactly how useful it will be.

- [12] F. Schweitzer, *Self-Organization of Complex Structures: From Individual to Collective Dynamics*, 1st ed. Amsterdam, The Netherlands: CRC Press, July 1997.

Edited collection of works broadly covering self-organization at many different levels, from single cells to economies. Part I looks at the evolution of complexity and evolutionary optimization. Part II goes from biological and ecological to socio-economic dynamics, including urban structure and traffic dynamics.

Papers that may be of interest for further study:

- Self-Organization Phenomena of Pedestrian Crowds, Helbing & Molnár
- Chaotic Behaviour of a model Plankton Community in a Heterogenous Environment, Steffen & Malchow

- [13] L. Tweedy, P. A. Thomason, P. I. Paschke, K. Martin, L. M. Machesky, M. Zagnoni, and R. H. Insall, "Seeing around corners: Cells solve mazes and respond at a distance using attractant breakdown," *Science (New York, N.Y.)*, vol. 369, no. 6507, August 2020.

**Self-generated chemotaxis:** Self-generated chemotaxis cannot be directly measured and typically requires computational modeling to analyze. It is distinguished from classical chemotaxis by several key features:

- Gradients are sharp, local, and nonsaturating (unlike traditional source/sink gradients).
- Diffusion plays a central role (in contrast to constant or linear gradients).
- General chemotaxis is limited in effective range (500  $\mu\text{m}$ ) and attractant concentration.

Cells such as *Dictyostelium discoideum* and metastatic cancer cells use self-generated chemotaxis to navigate complex environments (e.g., tumor tissue or migration routes). These cells degrade attractants locally using surface enzymes, resulting in dynamic gradients that help them sense and respond to upcoming junctions. This enables cells to "see around corners" and map their environment.

#### **Junction Navigation and Model Behavior:**

- In classical chemotaxis, cells choose paths randomly at junctions.
- In self-generated chemotaxis:
  - Paths are evenly split unless one is a dead end.
  - If a branch is a dead end, only a few cells explore it. Their degradation of attractants prevents others from following.
  - Short dead ends are completely avoided: attractant gradients are dissipated before cells even arrive.

#### **Maze Navigation:**

- Cells navigate mazes successfully even with uniform attractant concentration.
- Longer dead ends reduce decision fidelity.
- Decision-making improves over time due to attractant depletion in dead ends.
- Slower cell speeds (in simulation) improve accuracy, though this does not generalize to slower-moving cancer cells, likely due to differences in attractant diffusivity.
- Dead ends with widening or branching structures can create "chemotactic mirages" and attract cells.

**Key Conclusions:**

- Attractant flux (rate of change) is more critical for cell decisions than attractant concentration.
- Maze geometry, especially dead end length, affects gradient strength and navigational accuracy.
- Ligand breakdown is rarely modeled but is biologically significant and should be incorporated in future models.
- Implications for understanding complex migration phenomena, including:
  - Neutrophil extravasation,
  - Melanoblast migration in embryonic dermis,
  - Glioblastoma metastasis along white matter tracts.

**Modeling Details:**

- Simulations were implemented in Java.
- Diffusion was simulated using the semi-implicit DuFort-Frankel method in a complex environment.
- Cells followed a persistent, biased random walk informed by local gradient sensing.
- Gradient direction was estimated from grid points within  $6\text{ }\mu\text{m}$  of the cell centroid.
- Attractant degradation followed Michaelis-Menten kinetics, with rate  $r = v_{\max} \frac{c}{c + K_m}$ , where  $c$  is the local concentration and  $K_m$  is the Michaelis constant.

*Note:* This form of chemotaxis is fundamentally different from that used by *Physarum polycephalum*, which explores all paths and later prunes the least successful.

- [14] J. D. Wheeler and K. Y. K. Chan, “The Whole is Greater Than the Sum of Its Parts: Large-scale Phenomena Arising from Small-scale Biophysical Processes,” *Integrative and Comparative Biology*, vol. 63, no. 6, pp. 1399–1404, December 2023.