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A Rho GTPase based multi-cellular model explains spontaneous directional migration of neural crest cell groups

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During vertebrate embryogenesis, neural crest cells (NCCs) delaminate from the neural plate, becoming highly migratory through an epithelial-to-mesenchymal transition, and then travel long distances to invade target locations where they differentiate into a wide range of cell types. Coordinating this long range migration requires that NCCs integrate information from a variety of external signals, including chemoattractants. Surprisingly, a body of evidence suggests that chemoattractants may be dispensable for guiding NCCs in certain situations. Observations from *in vitro* experiments where NCCs are plated at the end of a fibronectin corridor, find that the collectives are able to migrate down the corridor with high persistence, in the absence of any directional information from an external chemoattractant[1]. Directional migration of the collectives was observed to be highly dependent upon the number of cells and corridor width, as increasing corridor width sufficiently while holding the number of cells constant could eliminate directional migration[2]. *In vivo*, groups of NCCs beginning their migration before budding of endodermal pouches, require the presence of chemoattractant Sdf1 (also known as CXCL12), sensed through filopodia, to successfully direct their migration, yet groups of NCCs beginning their migration after budding of endodermal pouches are able to migrate efficiently even when their filopodia are strongly antagonized, suggesting the pouches provide sufficient physical confinement as guidance[3]. Other *in vivo* experiments have observed that groups of NCCs transplanted to their target location are able to migrate in the reverse direction, suggesting that there is no existing guiding chemoattractant gradient providing migratory bias[4].

The existing hypothesis for this spontaneous collective directional migration suggests that it emerges due to two intercellular interactions between NCCs: contact inhibition of locomotion[5], and co-attraction[1]. Contact inhibition of locomotion (CIL) describes the tendency of NCCs to move away from each other upon contact, a process mediated by N-cadherins and the non-canonical Wnt signalling pathway, while co-attraction (COA) describes their ability to simultaneously attract each other through the autocrine production of the short-ranged chemoattractant C3a and its receptor C3aR. A particle-based model[6] was developed to support this hypothesis, but its recapitulation of spontaneous directional migration is likely due to the inertia experienced by the group, since the model is formulated with second-order mechanics equations ($F = m\ddot{x}$). More recently, a cellular Potts model was developed to support the hypothesis, but this result is also unsatisfying, since in addition to CIL and COA, the authors include a hard coded rule specifying single cell persistence to be lower than the persistence of cells in a collective. Thus in both models, cells are effectively endowed with a memory effect, whether implicitly through intertia or explicitly through high group persistence, explaining the observations of spontaneous directional migration without shedding much light upon how this phenomenon arises due to the interaction between CIL and COA.

This summer, we aimed to see if we could understand spontaneous collective directional migration, using a multi-cell 2D model developed over previous summers, in which contact inhibition of locomotion and co-attraction emerge from an underlying reaction-diffusion representation of Rho GTPase biochemistry. We

then tested the behavior of one, two and many cells in a two-dimensional channel. We find that the interplay between CIL and COA determines the overall behavior of the cluster. In particular, cells starting from one end of the channel will initially migrate toward the other end. These preliminary results seem to confirm the prevailing hypothesis by Mayor and coauthors[1, 5] that CIL and COA are major factors in collective migration of neural crest cells.

References

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