Mechanisms of Chain Migration: theory and experiment

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***Short Abstract* — Follow-the-leader chain migration is a striking cell migratory behavior observed during vertebrate development, and cancer metastasis, yet the mechanisms underlying the phenomena are unclear. One example of chain migration is displayed by the embryonic neural crest (NC). Here, we present a quantitative agent based modeling framework and two distinct model mechanisms to explain chain migration, using biological data from the embryonic neural crest (NC). We evaluate model mechanisms based on matrix and cell contact mediated promotion of chain migration. Our integrated approach offers a powerful means to test mechanistic hypotheses of chain migration mechanisms in an *in silico* framework.**

***Keywords* — chain migration, neural crest, agent-based model.**

I. Purpose

LONG distance cell migration involves directed and sustained cell movements that produce an ordered invasion of target sites. One of the more striking cell migratory behaviors observed in a wide variety of embryonic and adult model systems is follow-the-leader chain migration (*1-2*). Imaging advances permit the visualization of individual cell migratory behaviors during chain migration. However, while descriptions of the cellular features of chain migration have advanced, little is known about the mechanisms that regulate this intriguing cell migratory behavior.

One of the major long distance cell migration events in the vertebrate embryo involves neural crest (NC) cells (*3*). Neural crest cells delaminate from the dorsal neural tube midline and are sculpted onto stereotypical migratory pathways in a rostral-to-caudal manner throughout the embryo. Time-lapse and static imaging have revealed that NC cells travel as loosely connected, individual cells in a number of model systems including chick, zebrafish, and mouse. NC cells crawl through extracellular matrix and mesoderm with cell behaviors that include directed movement, contact-mediated guidance, and contact inhibition of locomotion. This suggests that multiple signaling mechanisms underlie NC cell migratory patterns.

Here, we consider two distinct mechanisms to explain follow-the-leader behavior using the NC as a model system. First (hypothesis 1), we consider a mechanism where cells follow a path of least resistance in the extracellular matrix (ECM), forged by a preceding cell or cells. Second (hypothesis 2), we consider a mechanism where cell filopodial interactions provide contact guidance that direct trailing cells to follow a lead cell. -

To investigate the role the proposed mechanisms play in the persistence of NC cell chain migration as well as to help direct future experiments, we developed a set of agent-based computational models capable of simulating cell migration in a 2-dimensional domain (5). Chain migration persistence was measured in each model under different parameter conditions. Using perturbation analyses we found that chain migration persistence requires a high degree of directional bias in both lead and follower cells towards the target. Chain migration persistence was also promoted when lead cells maintained cell contact with followers, but not vice-versa. Finally, providing a path of least resistance in the ECM was not sufficient alone to drive chain persistence. Our results indicate that NC follow-the-leader behavior depends on the interplay of directional cell movement and biased cell–cell contact.

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