Neural Crest Cluster's Movement Speed Changes Inside Channels with Different Width

Background

Neural crest (NC) cells are a migratory cell population synonymous with vertebrate evolution. They generate a wide variety of cell and tissue types during embryonic and adult development including cartilage and bone, connective tissue, endocrine cells as well as neurons, and many others[1]. Understanding the mechanism of their migration as small clusters is an influential study and has attracted many researchers. Shellard et al. used live imaging, ablation, and numerical modeling methods to prove that supracellular contraction at the rear of neural crest cell groups drives the cluster's collective chemotaxis[2].

While Shellard et al. demonstrated how neural crest cells move by the contraction at the rear, their model focused more on the collective behavior resulting from intracluster force interactions and has no boundary for cell movement. However, when neural crest cells migrate throughout the embryo, they often face some kinds of geographic confinements. One example of cell migration with confinement is channel-like movements. Channel-like cell migration could be found during the development of cellular tubes, such as the formation of blood vessels and trachea, where contractile cells to the rest of the cells behind them. Neural crest cells that are capable of moving with stable cell-cell adhesions, such as cranial neural crest cells, would likely display the channel-like movement pattern.[4]

To investigate how channel-like migration is affected by the channel width, we built up on Shellard's numerical model while adding a channel constraint subpart to the force equation.

Rationale

The neural plate interacts with the presumptive epidermis and forms NC cells at its borders. After the formation of NC cells, the NC cells migrate to different parts of the body by moving through a niche between the neural tube formed by the folding of the neural plate and ectoderm.[3] Therefore we want to test whether NC cells will move differently when they are inside channels and if the size of channels causes differences in the speed or other moving patterns of the NC cell cluster movement by using the same rationale and coding of the neural crest cluster model.

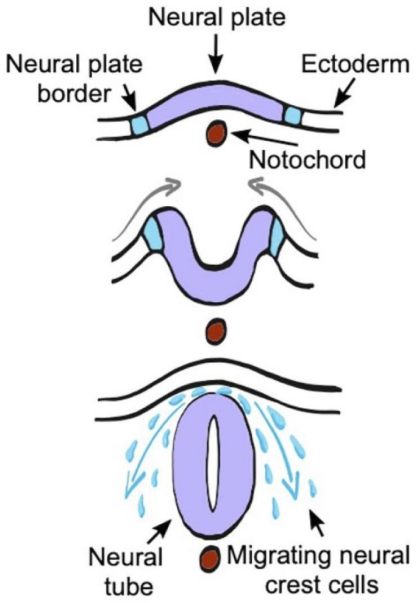


Figure 1. The formation of the neural tube and migration of the neural crest cells. ***On the Potential Role of the Neural Crest Cells in Integrating Pigmentation Into Behavioral and Physiological Syndromes, by LM San-Jose, A. Roulin (2020).***

In order to simulate the real condition inside the channel, we built two virtual walls at the top and bottom. These walls were being set as impermeable and will generate a force with the same amplitude while flipping the direction when it receives a force from the NC cells. For instance, if one cell pushes the wall with a force of 30 degrees, the wall will rebound the cell back with the same force but in another 30-degree direction (Figure 2).

Figure 2. Example of the interaction between the channel wall and NC cells after NC cells hit the channel wall during movement .

In mathematical terms, we add a directional vector to Shellard's original model equation. The determination process of cell-cell interaction force f_i, self propulsion f_p, stochastic noise f_n, as well as the dampening δ remains unchanged as compared to the original equation. The $u(y)$ component refers to cell movement directional change when reaching the virtual channel. Under elastic collision conditions, where kinetic energy is completely conserved when an individual cell reaches either the top or bottom channel broader, set as $width$, the original force balance equation would be cross produced with $u(y) = [1, -1]$. Since the cells in the model is moving horizontally, bouncing to the channel would result in a flip of the y component of the force.

$$\frac{\Delta v}{\Delta t} = \sum_n f_i(a,n) + f_p(a) + f_n - \delta v_a$$ Shellard equation

$$\frac{\Delta v}{\Delta t} = u(y) * \left[\sum_n f_i(a,n) + f_p(a) + f_n - \delta v_a\right]$$ Our equation

when $-width < y < width$, $u(y) = [1, 1]$

when $y < -width\ OR\ y > width$, $u(y) = [1, -1]$

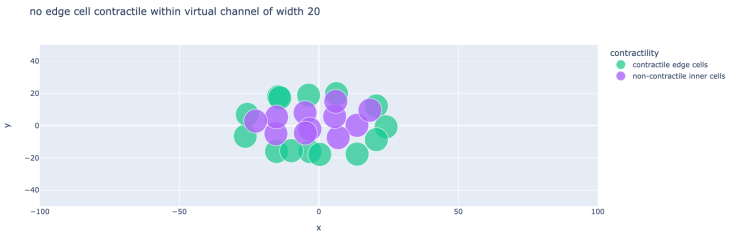
Since all cells' positions were generated randomly at the beginning, we observed that the speed of NC clusters was not uniform even if we kept the width of the channel constant. To minimize this error, we repeated the measurement of speed 10 times under each width we chose and took the average speed for analysis.

Results

First we tested if adding a channel constraint would affect the overall speed of the cell cluster. When the cell cluster was simulated in a channel while no rear cells were set as contractile, the cluster does not demonstrate significant horizontal movement: after 300 timesteps, the cluster center is still around the origin, which is the starting position of the simulation (Figure 3A). Therefore, the channel itself will not cause the cell cluster to move. Then

we set one side to be contractile to observe the behavior of the cluster. When cell cluster movement was only affected by the interaction forces within cells such as repulsion and contractility, it moved with a speed of 2.50 unit/timestep (Figure 3B). We next built a virtual channel mimicking the niches that the NC cells move through in the biological system. The cluster distribution was spatially limited to 20 units which was the width of the channel that we built (we use the width to represent both the upper half and lower half of the channel limit, so in this case, the width total is actually 40 units). Since we knew that the edge of the NC cluster tends to move outside the 20 units boundary, this wall width indicates that the virtual channel effectively interacted with the cell cluster (Figure 3C). As a result, the cell cluster moved slightly faster as compared to that without a channel, as the slope of position change for the cluster within the channel is greater (Figure 3D).

A



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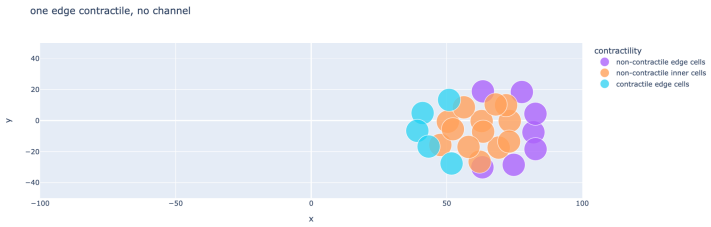

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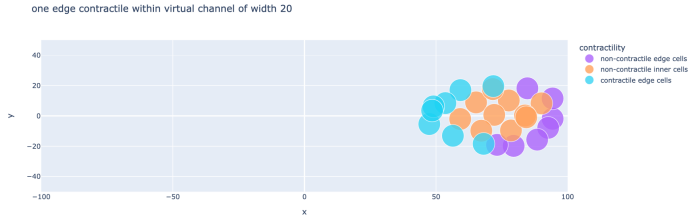

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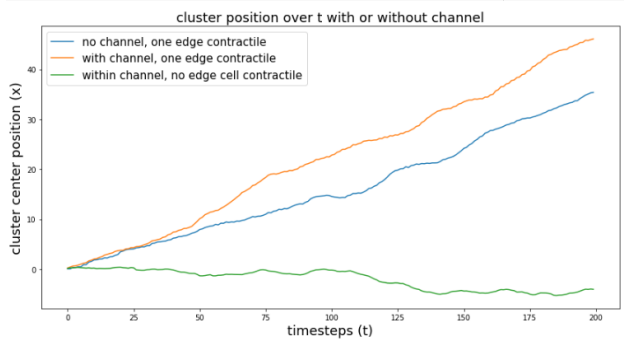

Figure 3. Animations of a 25-population NC cell clusters movement without boundary and inside a channel of 20 width respectively after 300 iterations. The y-axis is the channel width and the x-axis is the distance of the movement for A,B and C. The cell cluster in Figure 3 B has some part of its edges outside the 20 units boundary while the cluster in Figure 3 C is restrained inside the channel. The rear motor cells are shown in blue.

Next, we tested the movement of the cell cluster in four channels with different channel widths, 6, 10, 20, and 50 units. As channel width increases, the average moving speed of the cell cluster decreases (Figure 4). Average speed is calculated as the average magnitude of the velocity of the cells in the cluster at each iteration. When the channel width is increased to 50 units, the cell cluster no longer interacts with the channel borders since the scale of the channel is larger than that cell cluster can reach during its movement; therefore, the moving pattern and speed are similar to cell clusters with no channel. Furthermore, as channel width increases, the scale of average speed variation decreases. This is intuitively correct: as the confinement is looser, the cells would be less likely to bounce to the walls and thus would have less significant speed change between iterations.

Figure 4. Four speed graphs for the NC cell cluster under 6, 10, 20, and 50 width units respectively. The y-axis is the speed and the x-axis is the timesteps of the movement. The average speed for the cell cluster inside the channel with width 6 is 2.99 unit/timestep; with width 10 is 2.87 unit/timestep; with width 20 is 2.52 unit/timestep; with width 50 is 2.50 unit/timestep.

Discussion

Using the numerical model developed from Shellard's group, we demonstrated how the speed of the neural crest cluster will be affected by the width of the channel. Our study provides a possibility that other cell clusters may behave similarly to the neural crest when they are moving inside a channel. With this numerical model, researchers can further study different types of cells which constantly travel inside tissues.

As we performed the experiment, we realized the width of the channel cannot be fewer than 5 units which is the original width range set for the cell distribution. To avoid damaging the cluster integrity, we did not force the cell cluster to be inside a channel with a width fewer than 5 units. Further study can be made to test whether cell clusters have the ability to squeeze into a channel of width much smaller compared to the cluster itself.

We also came up with some branches of the question we chose. We wondered whether the elasticity of the channel wall may also affect the speed of NC cell clusters. In our experiment, we set that the force will not be lost after the cell cluster touches the wall; while in the real case, it is usually more complicated. In different tissues, there can be walls that absorb the kinetic energy from the cells bumping into them, or channels that act as a trampoline and give cells energy to make them move faster. Apart from that, the channel used in our experiment is made of parallel walls, but it is also possible for the two walls to be nonparallel. The channel can have the appearance of a funnel where the space starts to decrease as the cluster moves along the channel. We also observed that if we add more cells into the cluster to make it larger, they would move slower than a smaller cluster. These could all be interesting topics for later studies.

References

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