

RESEARCH REPORT

Development of a cell motility model coupling Rho GTPase biochemistry with cell geometry

Brian Merchant ^{*1}

¹University of British Columbia, Canada

SUMMER 2014

1 Introduction

Starting in February 2014, I began a guided reading project under the supervision of Professor James J. Feng, which became a research assistantship in May 2014. Work on our project continues, but this document summarizes work we did between May 2014 and September 2014.

2 Differential Adhesion Hypothesis

Thoughts we had regarding the “Differential Adhesion Hypothesis” (DAH) and its variants (e.g. “Differential Surface Contraction Hypothesis” or “Differential Interfacial Tension Hypothesis” (DITH)) prompted us to set off on our current explorations. We noted that DAH attempted to encapsulate many of the intricacies of cell-cell interactions into a single, spatiotemporally static concept: “tissue surface tension”. These intricacies include concepts such as: regulation of cell-cell adhesion (cell attraction or repulsion), differences in cell motility between tissue sub-populations, or biochemical polarization of tissue sub-populations. Due to this broad abstraction, experiments often provide observations which cannot be simply explained via DAH (for example, different behaviour *in vitro* compared to *in vivo*). Additionally, experimental attempts to measure tissue surface tension are mired with issues regarding interpretation of the data.

Another popular concept which can often be seen hand-in-hand with DAH was that of “energy minimization”. In order to explain the relevance of DAH to various scenarios, modellers commonly construct computational experiments where an energy function, based on

*b.merchant@ugrad.math.ubc.ca

force interactions inspired by DAH or DITH, is minimized using a Monte Carlo or Markov-chain based method (for example, Cellular Potts Models (CPMs)). We identified two important criticisms with these modelling methodologies: 1) developing an energy function from an abstract concept such as DAH/DITH is difficult to interpret physically and 2) there is no connection between the kinetics of a Monte Carlo method based model and actual biological kinetics, although the two are often taken to be equivalent in CPMs.

In order to come up with a framework that had greater explanatory power than DAH, we thought it would be beneficial to find a biological case where DAH or its variants had not been applied to date, and more importantly, where the analogy that DAH took inspiration from (liquid segregation due to differing surface tension) was difficult to relate to the biological phenomenon in question. However, this phenomenon would still have to have some similarity to other cases where DAH is deployed: in particular, it would be helpful if some segregation or cell sorting like phenomenon occurred.

Identifying such a phenomenon and attempting to model it would mentally force us to abandon old analogies and developing instead a new mode of thought. Then perhaps we would find that this new mode of thought might be relevant to previously well studied examples where DAH had already been deployed as an explanation.

3 Why Neural Crest Cell (NCC) migration?

After exploring various candidate phenomena (for example, the patterning of cones on an animal retina), we thought that neural crest cell migration fits many of the requirements of a biological phenomenon that would fit our goals. Neural crest cells are highly migratory and contribute to many parts of the development of an organism. Specifically then, we chose to study cephalic neural crest cell migration from the rhombomeres to the branchial arches (see Figure 1), for reasons I will now discuss.

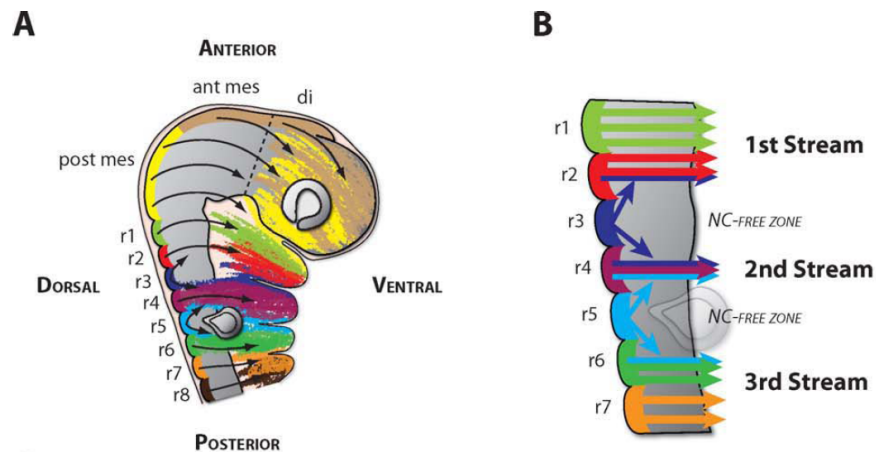


Figure 1: A) : Overview of the cephalic neural crest migration. CNC cells invade their surrounding tissues in register with their original location along the AP axis. B): Detailed view of the early phase of CNC migration during which anterior and posterior migration of cells from r3 and r5 give rise to NC-free regions adjacent to the neural tube.

Cephalic neural crest cells migrate from the rhombomeres (where they develop) down to the branchial arches, where they are subsequently involved in the development of the heart, and various connective and nervous tissue. As they migrate down towards the branchial arches, neural crest cell populations from specific rhombomeres maintain segregation even if they are adjacent. Deploying DAH as an explanation is difficult, as the migratory streams have transient intercellular contact between members, unlike in epithelial tissue. Thus while an argument suggesting differential “surface tension” between two migrating streams could be thought of, it is simpler to consider the cell-level interactions between the streams that lead to stream organization. Furthermore, the kinetics of a candidate model has to capture not only the segregation between these cell populations, but also their movement down the migration-permissive corridor. Data from experiments exist regarding the time it takes for NCC streams to traverse migratory pathways, and comparing model results with such data would be helpful in fine-tuning parameters. However, such comparisons generally cannot be carried out with energy function minimization based models.

Suitable model kinetics are readily inspired by a single underlying biological phenomenon: that of cell polarization. Cell polarization is required for the migration cells in general, and is further regulated in group organization in order maintain effective movement conditions. For instance, cell-cell contact inhibition allows cells (“contact inhibition of locomotion”) to migrate without continually interfering with their neighbours. Thus, we think that the regulation of cell polarization is likely the underlying phenomenon in stream segregation.

4 Modelling work undertaken to explore NCC migration

Over the summer, we worked on developing a single-cell model that would:

1. capture Rho GTPase spatial polarization in order to model cell polarization during migration;
2. be flexible enough to allow us to encode cell-cell interaction rules based on regulating cell polarization and;
3. be simple enough to use for multicellular experiments in the future.

We were successful in this effort over the summer, and continue to refine that model. In order to produce as simple (yet useful) a model as possible, we have discretized the circumference of the cells by nodes connected by elastic membranes, and thus reduced a partial-differential-equation system to ordinary differential equations evolving on the nodes. This has led to preliminary results that are highly promising.

5 Conclusion

In summary, we developed a modelling framework that allows us to consider biological phenomena where the underlying biological kinetics are too dynamic to be reasonably simplified

by hypotheses currently popular amongst biophysicists. The model has produced interesting results in several simplified test cases, and we are in the process of applying it to more realistic conditions