Cell Motility
Progress Q1 2010

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1. Summary

As called out in the Cell Motility Deliverables document for this quarter [1], we have implemented primitives in the platform to support active cellular shaping and directed movement and have developed models to demonstrate these new features. In particular, we have implemented a "reach" mechanism by which a cell can form adhesions over an extended distance. As a complementary supporting feature, contact signal exchange between adhered cells has also been implemented, allowing cells to exchange signals with adhered neighbors despite possible physical separation. These features have been demonstrated in two models so far, with an additional model in development. These models correspond to the use cases described in the deliverables document [1].

Deliverables called out but not yet implemented include movement rules relative to a cell's center of mass ("expand" and "contract" rules) and an ad hoc cell relocation tool. In the first case, the potential uses and functionality largely overlap the implemented "reach" functionality which is still being explored. In the second case, a general-purpose simulation checkpoint editor is in development that will eventually enable detailed ad hoc cell manipulations including physical relocation.

2. Adhesion "Reach" and Signal Exchange

In the deliverables document, we proposed that each adhesion rule might have an associated fixed or resource-dependent "reach" for forming new adhesions. Conceptually, this would be like a cell having different kinds of pseudopodia for each kind of adhesion it might form. We decided, therefore, to instead make Reach a cell property, like Rigidity or Elasticity. Unlike previous cell properties, however, Reach is evaluated for each cell subunit independently during adhesion formation. Adhesion breaking distance was likewise proposed as being configurable per adhesion rule. We believe this concept remains valid as different adhesions may have different resiliences when stretched, though we have not yet implemented this feature. However, because adhesions have at least one step in which to act and adhesion strengths vary with the concentrations of adhered resources, we have not yet missed this feature. Reach, then, is currently acting in the role of extending both adhesion formation distance and adhesion maintenance distance.

For a cell to be able to recognize and respond to an adhesion formed over an extended distance, some form of signal exchange between adhered entities is required. We had originally proposed that all surface signals be automatically exchanged between adhered entities as if they were in contact. However, in order to distinguish between adhesions that involve substantial cell membrane contact and those in which the mechanism of adhesion does not include meaningful membrane contact, each adhesion rule can be configured to either exchange or not exchange surface signals over adhesions based on that rule.

Two models have been developed to demonstrate cell motility using these new features. The first model is based on the "crawling-by-rolling" concept presented in the deliverables document and illustrated in Figure 1. In the proposed model, an environmental gradient polarizes a cell and increases adhesion reach in the leading edge subunits (blue), initiating a forward roll. As the cell moves within the gradient, it re-polarizes and the process repeats continually.

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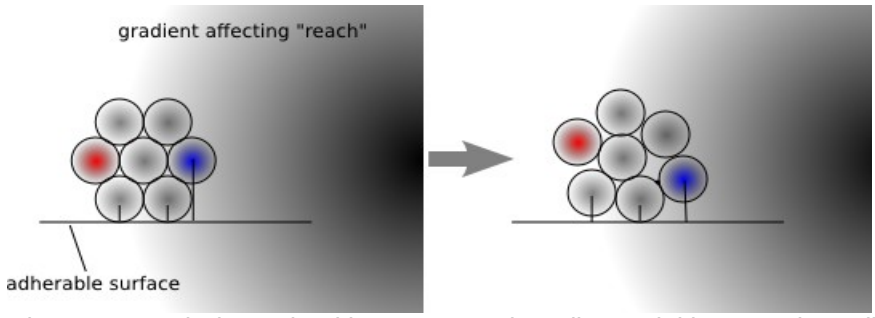

Figure 1: Reach determined by an external gradient to initiate crawl or roll.

The model we developed is similar but uses a fixed reach distance and depends on varying the strength of adhesions between the leading and trailing subunits of the cell. This change helped reduce occurrences of the rolling cell's subunits with excessively long reach forming adhesions with subunits deep in the underlying substrate. Adhesions formed with deeper subunits can cause the cell to embed itself into the substrate – a potentially interesting mechanism for modeling an invading cell, but undesired for surface crawling. As showing in Figure 2, differences between the adhesion strength in leading and trailing edge subunits enables chemotactic crawling in the model cell.

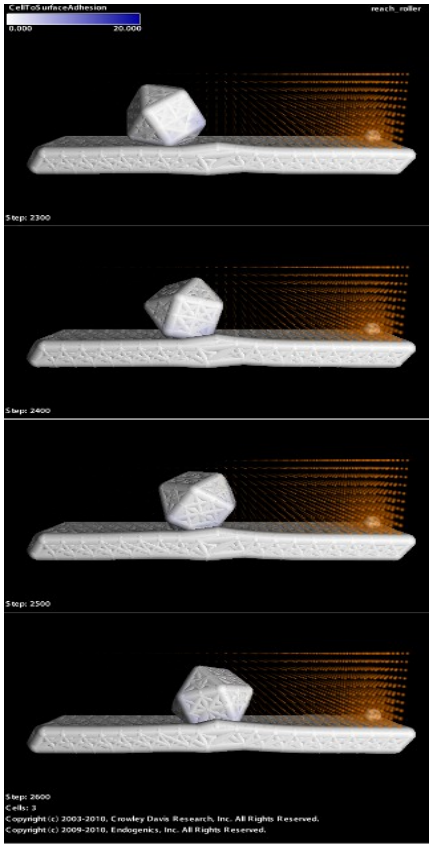

Figure 2: Adhesion "Reach" enables chemotactic crawling

Modeling a cell spreading itself on a surface using adhesion reach was also proposed in the deliverables

document, as illustrated in Figure 3. We made two versions of this conceptual model.

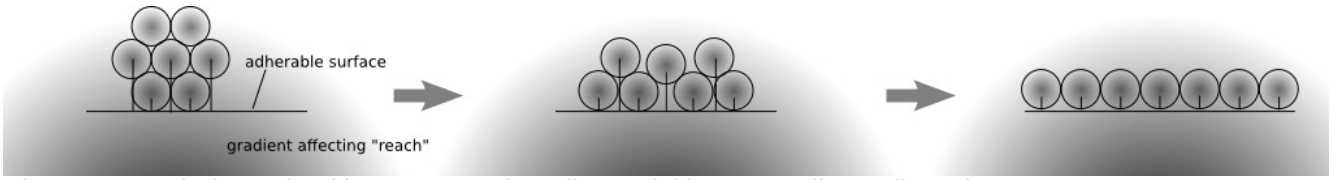

Figure 3: Reach determined by an external gradient to initiate spreading or flattening.

In the first model, shown in Figure 4, we varied both reach distance and adhesion strength and used signal exchange over adhesions. This model placed the spreading cell on an underlying substrate similar to the one under the crawling cell. To prevent the cell from reaching through the substrate and pulling itself in, it reduces its adhesion strength and reach when adhesions are maintained over time. This reduction in adhesion strength combined with the relatively rough substrate surface limited flattening.

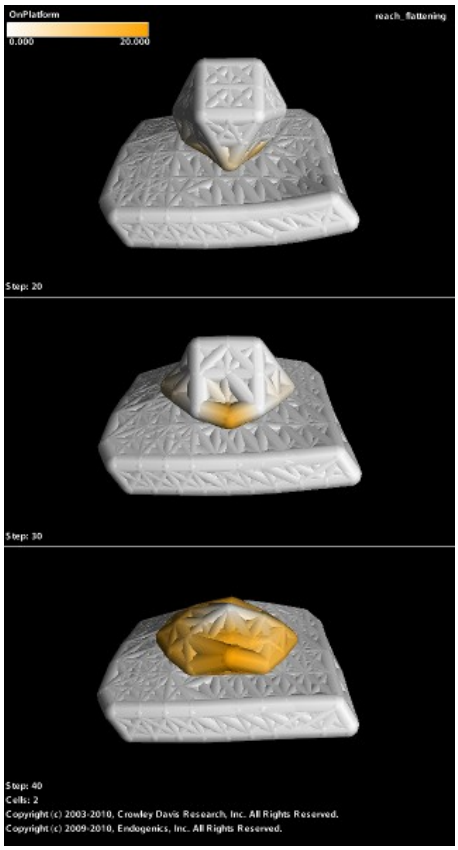

Figure 4: Adhesion Reach to flatten a cell

A second cell flattening model attempted to maximize flattening by replacing the penetrable substrate with a very large, single-subunit cell, acting as an adherable fixed sphere. In this simpler model, there was no need to vary adhesion reach or strength and in combination with the smoother underlying surface, greater flattening was achieved as shown in Figure 5.

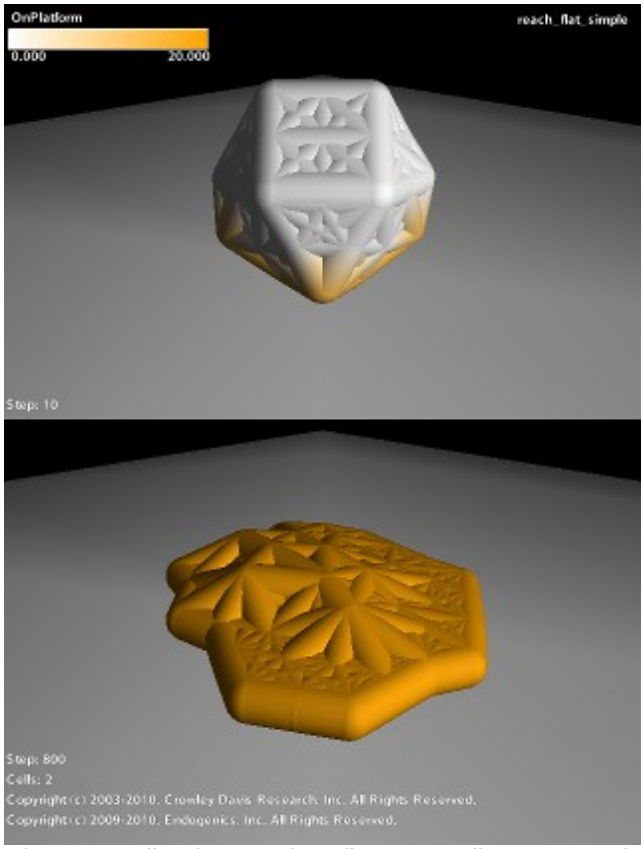

Figure 5: Adhesion reach to flatten a cell on a smooth adherable surface

3. Motility Application: Wound Closing

We have begun work on the wound-closing model proposed in the deliverables document and illustrated in Figure 6. However, undesired adhesions formed between neighboring cells on the same side of a wound are dominating the model, preventing adhesions across the wound from forming and achieving the desired effect as shown in Figure 7. Pathways to neutralize undesired adhesions while maintaining desired adhesions will need to be explored.

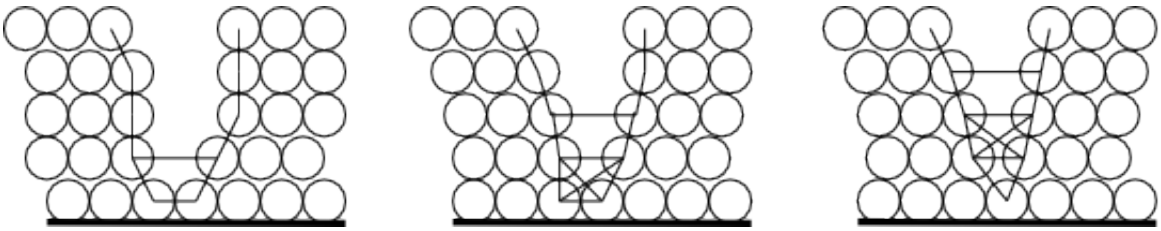

Figure 6: Wound edge cells forming adhesions with nearby edge cells enables active wound closing

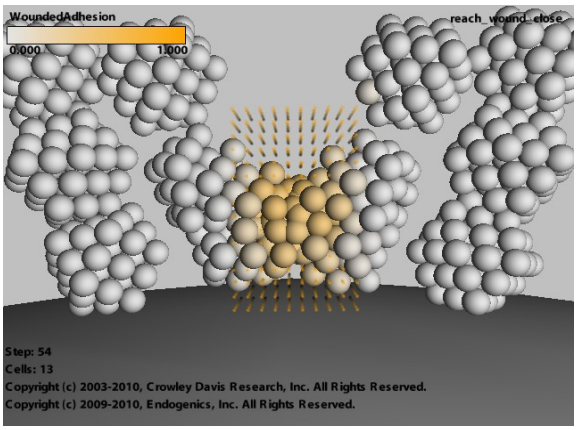

Figure 7: To date, wound-closing model tears itself apart

4. Next Steps

With adhesion reach and signaling having already demonstrated their utility, there is little immediate demand for a largely duplicate method of adhesion search via expansion and contraction. That mechanism, then, is being set aside while the limits of reach are explored. Our attention currently is turned to active shaping leading to more canonical cell shapes such as cuboidal, columnar, and squamous. In particular, achievement of squamous cell shaping is much desired for the epidermis model.

Work continues on a general-purpose simulation checkpoint editor that would provide the foundation for ad hoc cell relocation as called out in the deliverables document. A separate, one-off tool for this purpose, then, will not be attempted and we will simply keep pressure on the general tool to support this functionality.

Work has also begun to develop fitness functions suitable for finding models with motility features through evolutionary search. Initial test cases have produced flattening models similar to that of Figure 5.

5. References

1. Habig, J. et al. (2010) Cell Motility Deliverables Q1 2010. Internal report for Crowley Davis, Inc.