Mammary Acinus Modeling/ Manuscript Preparation: Sept 2010 update

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Introduction:

Early in September 2010 we began in earnest to approach the TATRC milestone of preparing a “paper that describes (the) computation platform and its application to tissue modeling submitted to a peer-reviewed journal” (TATRC Project milestones). The purpose of such a manuscript, besides the obvious goal of documenting what we have accomplished, is to produce a paper that can be cited by others with regard to the modeling approach, what we have called “what the system can do”, where “system” includes modeling, data export and analysis, experimentation, evolutionary search and automated methods, among other capabilities. In addition, the specific biological subject matter of such a paper, mammary acinus (MA) development and its potential disruption by oncogenes, and the methods used to study such development could also be useful to other investigators or lab groups.

We began planning a manuscript with the starting point of the MA model that had emerged from our recent discussions with Cheuk Leung at HMS, primarily because he was one person we could immediately identify as benefiting from such a paper. However, it soon became very clear that this model was ill-suited to the above purposes because its structure and underlying assumptions did not square with the mammary acinus literature as a whole; instead, it seemed rather idiosyncratic and unbalanced in its representation of core biological processes. More than this, that model was being run in a 1.04 release client and server, which is not compatible with later versions, notably the Endogenics client with its visualization capabilities and the current 1.08 and 1.09 releases with their enhanced features. In view of this, we began to build new models that are more consistent with the consensus in the literature regarding mechanisms of MA development, that run on the latest releases, and some of which incorporate platform capabilities that heretofore had not been built into earlier generations of MA models (e.g., active cell shaping, signaling nodes, and cell “reach” to help close gaps with neighbors to make a tighter cluster).

We are now approaching a basic characterization of development in a 1.09 version model that behaves qualitatively in a similar manner to the original 1.04 MA model: that is, it grows rapidly to form a solid ball of ~100-120 cells, stabilizes, and then becomes hollow by death of ~30 inner cells, leaving a hollow ball containing~80-90 cells surrounded by matrix. The remainder of this report describes this model and it outlines our plans for further model development and experimentation that, if completed, we are confident would lead to a manuscript worthy of submission to a peer-reviewed journal. Having said that, though, we must acknowledge the possibility that unforeseen hurdles could prevent us from reaching that goal using our existing servers, clients, and platform capabilities. If so, further platform modifications, bug fixes, or performance enhancements may be necessary.

Research results:

In the basic model (summarized in Figure 1), matrix contact drives three pathways, survival, cell proliferation (growth and division), and maturation.

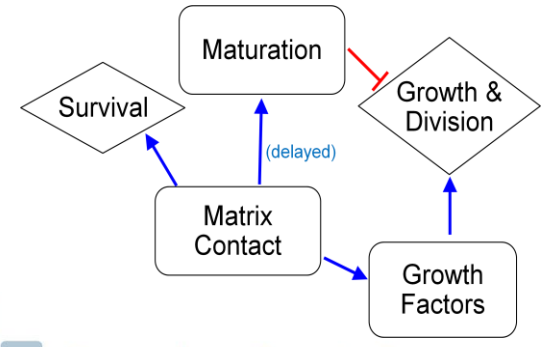


Figure 1. Conceptual diagram for basic acinus model. Blue arrows indicate, "Promotes, leads to or causes”; red termini indicate, “Inhibits or prevents”. Achieving the state of maturation is delayed.

Upgrading this model from 1.04 to 1.06 (to take advantage of the Endogenics client's visualization capabilities and prepare for further changes available in later releases) was not trivial. The three effect values of Matrix Contact on Genes 2, 3, and 4 had to be readjusted, and because these drive the model behavior, it turned out that tuning them was extremely sensitive to minor changes. This situation points out that the model is rather fragile, as we suspected it might be, given that one of the major drivers is essentially a timer and binary switch via Gene 4 leading to Maturation. Once [Maturation] exceeds [Maturation Threshold] Division is progressively diminished and then shut down altogether. As long as cells remain in contact with Matrix, this situation persists.

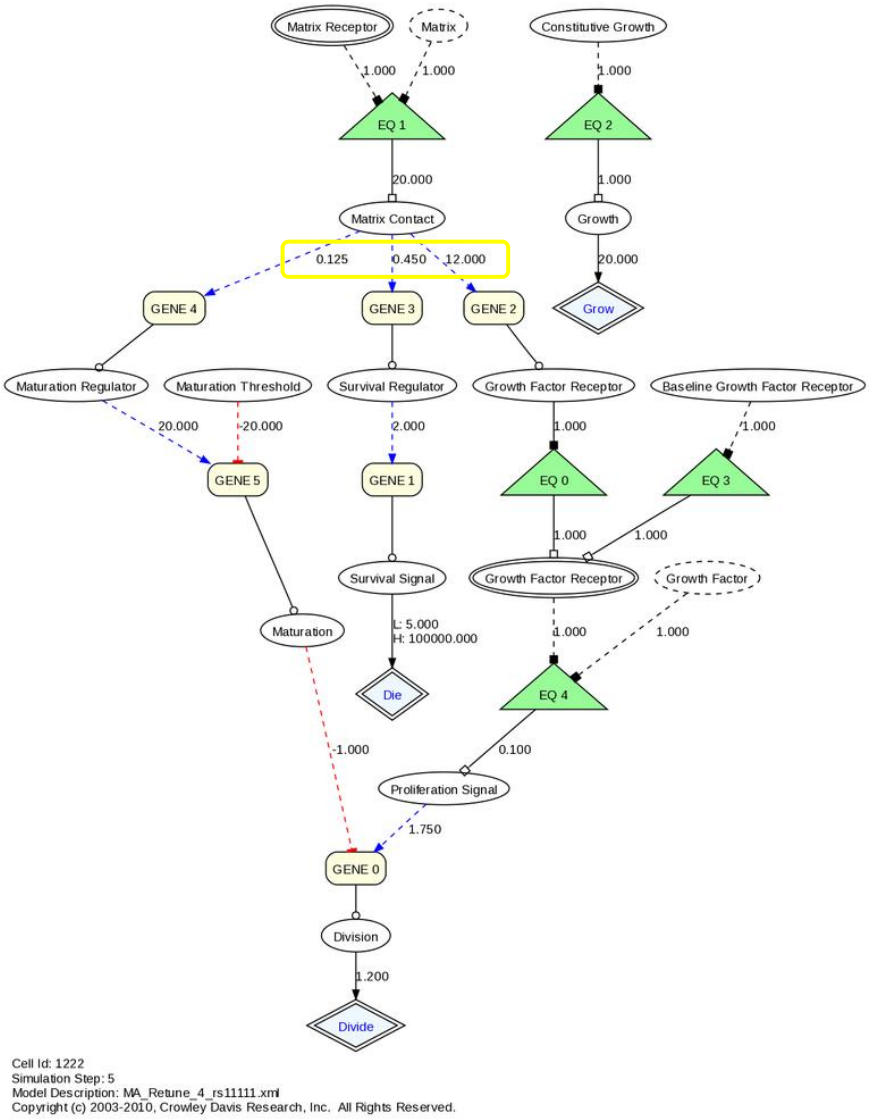


Figure 2. GRN for basic MA model. See text for details.

As we completed these model changes, we also began to design an evolutionary search strategy to evolve suitable settings for these three Matrix Contact-driven effect values, starting with a detuned model

where all three effect values of Matrix Contact on Genes 2, 3, and 4 = 1.0. Under these conditions, the initial acinar cell does not divide, and no development occurs.

Our main goal in these studies was to use the GA to find suitable values, based on matching the end phenotype to the endpoint of our hand-designed model. It turns out that this type of GA search is not as simple as one might expect a priori, and especially if one is to ensure that the right kind of balance is achieved among the three controlling pathways as the acinus reaches stability. In fact, our current assessment is that such a search may be impossible with our current GA capabilities, because of the narrow range of effect values in which normal development occurs, and because of the abrupt changes in MA behavior and morphology when the values fall outside of this range.

Because of these obstacles, we turned our attention away from evolving a network capable of driving normal MA development, and instead began to consider other experiments that could take advantage of the automated search capabilities of the GA, along with descriptive metrics for MA morphology based on difference distributions. Rather than use these methods to conduct a search process, we have begun to apply these techniques toward evaluating the phenotype space of MA models (Figures 3 -5).

(see next page)

We also anticipate that the paper would include three main branches or lines of inquiry beyond the basic model design, description of the development process, and analysis of the phenotype space. These branches, summarized diagrammatically in Figure 7, are as follows: robustness of development to gene promotion noise; incorporation of autocrine/ TGFβ-like pathways for curtailing proliferation, instead of the timer mechanism outlined above, and analysis of oncogene experiments analogous to those reported in the literature.

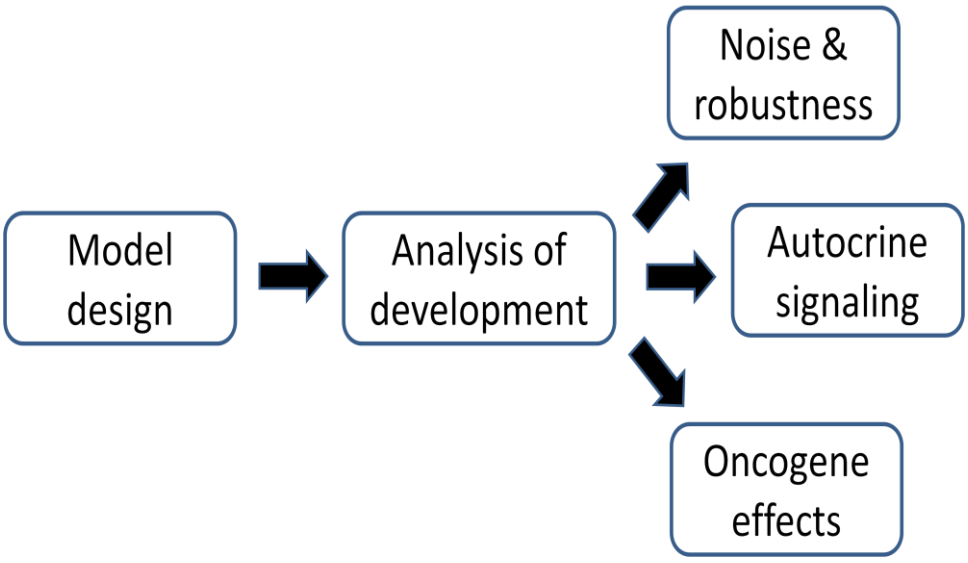
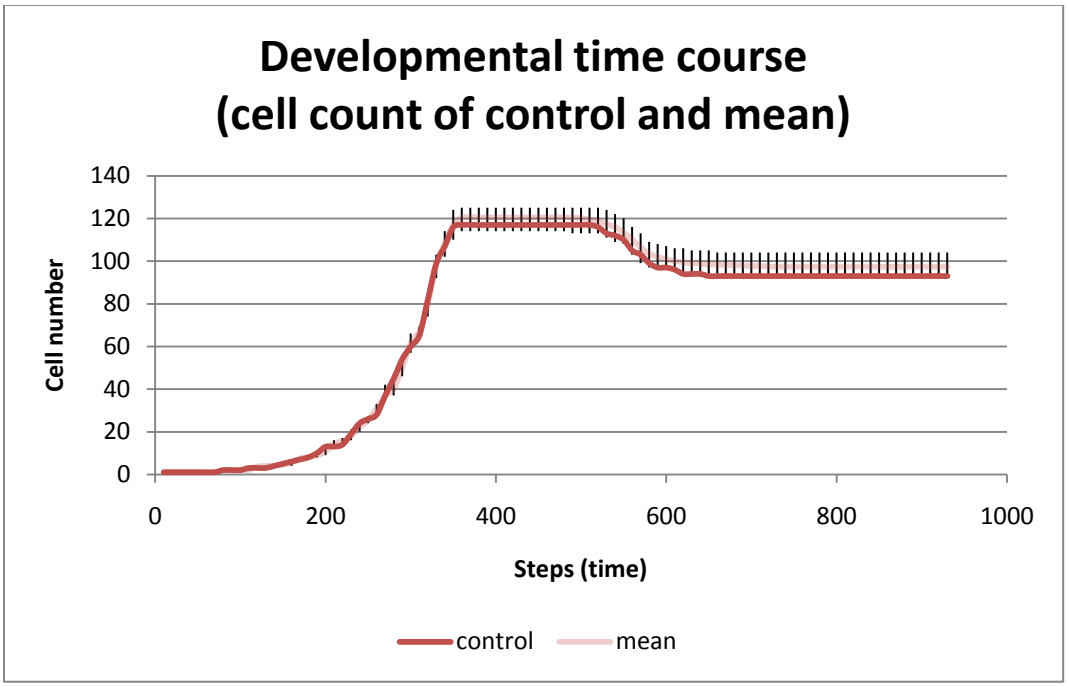
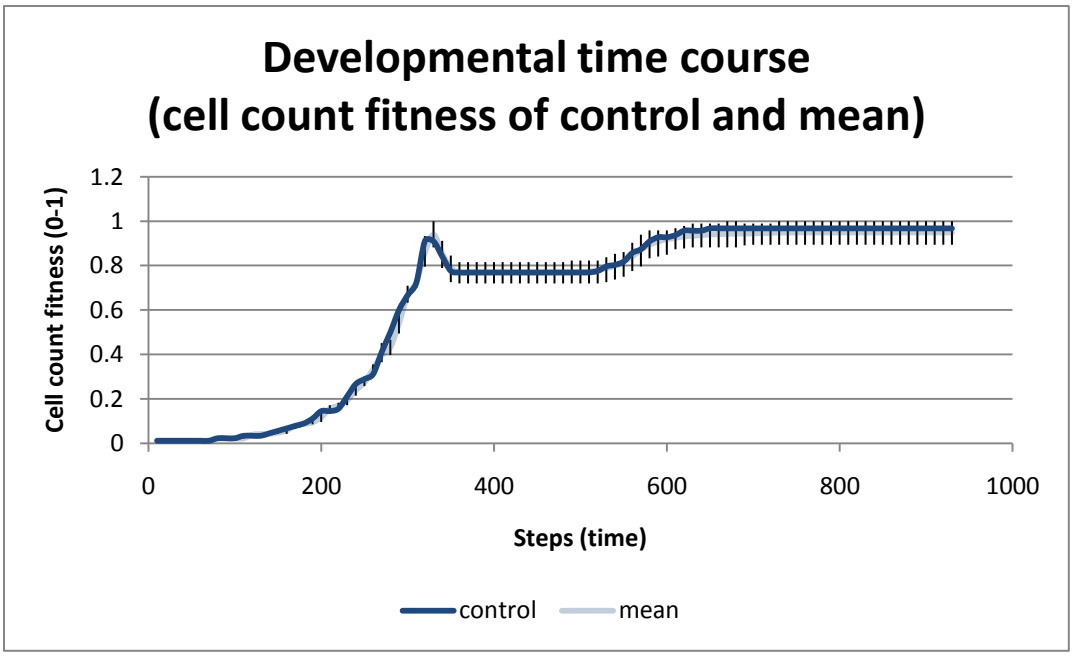


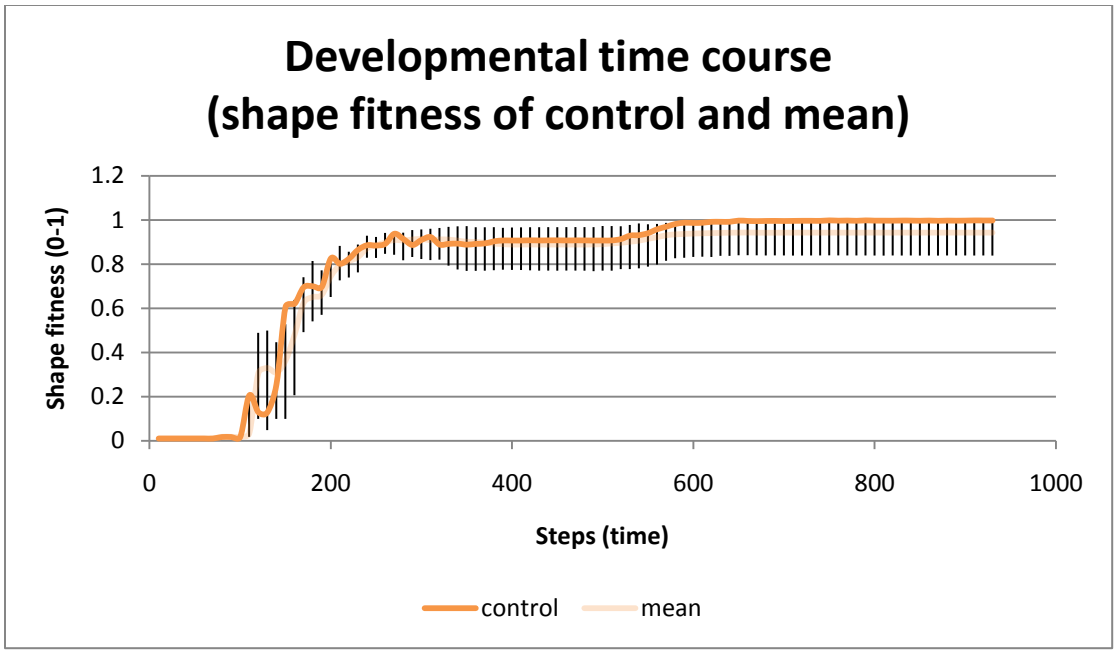
Figure 7. Schematic for manuscript. The basic model design has been established and analysis of development, including phenotype space, has begun. The remaining topics have not been addressed in experiments.

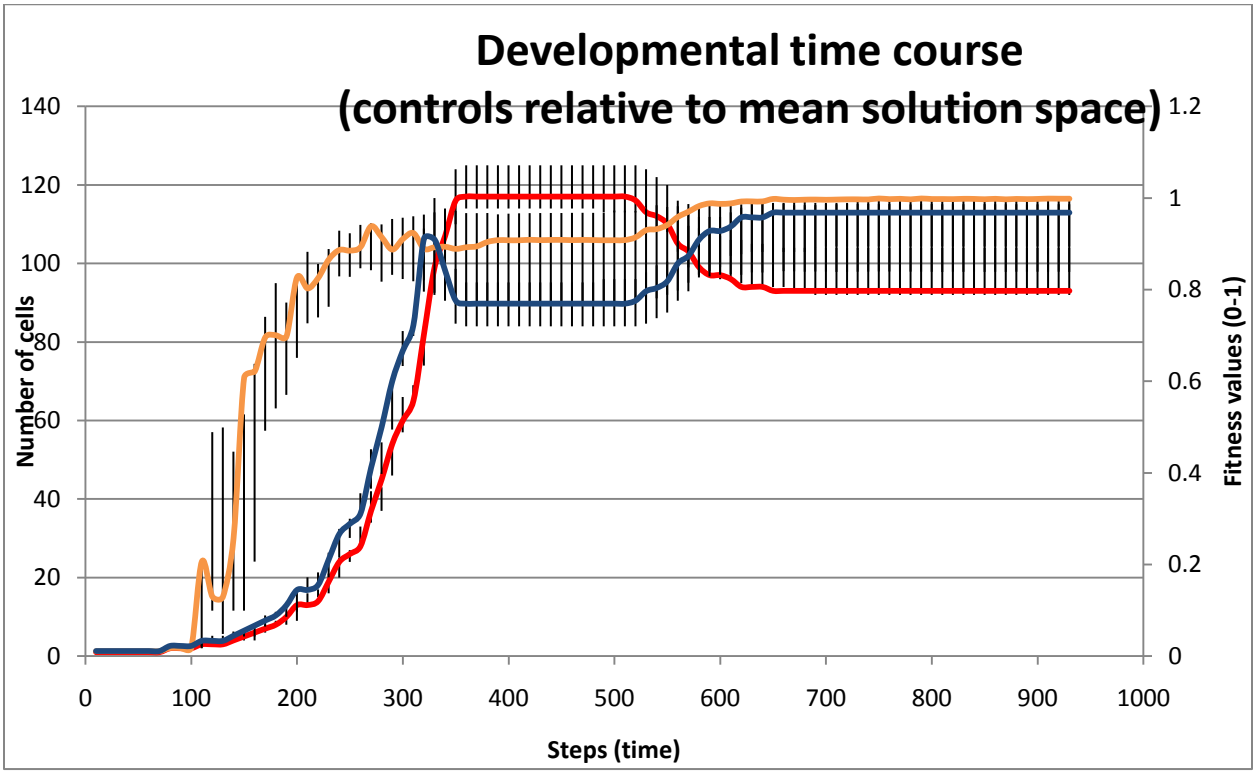
Figs 3-6 next page.





Figures 3 & 4. The phenotype space of developing virtual MAs. Cell count (Fig 3, upper) and cell count fitness (Fig 4, lower) relative to a particular target reveal the variability of morphology among 24 runs.





Figures 5 & 6. Shape matching metric (Fig 5, upper) and composite of Figs 3-5 (lower, Fig 6) illustrate the developmental variability of MA morphology in 24 simulation runs.