Boundary formation in developing tissues – a mathematical model for inter-cellular inductive Notch signaling

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In developing tissues, when cells expressing two different factors are juxtaposed under specific conditions, they give rise to a boundary of specialized cells. This phenomenon has been identified at the dorsoventral cell boundary during the development of drosophila wing disc, at the Apical Ectodermal Ridge (AER) of the vertebrate limb, and at the boundary between neural and non-neural ectoderm in neural crest formation. Specialized cells form at the boundary of Fringe expressing and Fringe non-expressing cells by a specific type of Serrate→Notch / Delta→Notch interaction, called as inductive signaling. The presence of Fringe is said to inhibit the binding ability of Serrate ligand to Notch and enhance that of Delta to Notch. Although several of the signaling elements have been identified experimentally, it remains unclear how the inter-cellular interactions can give rise to such a boundary of specialized cells. Here we present a simple ordinary differential equation (ODE) model involving Delta→Notch and Serrate→Notch interactions between juxtaposed Fringe expressing and Fringe non-expressing cells. When this ODE model is incorporated into a 2D spatial arrangement of cells using cell-based modeling environment – Compucell3D and SBML based ODE solver called Bionet solver, it shows that a boundary of specialized cells forms which expresses a higher level of Notch than the others. We analyze this model both analytically and numerically showing the conditions under which such a boundary is formed as observed in living systems. In addition, we also incorporate this model into a 3D cellular arrangement and show the formation of Apical Ectodermal Ridge in vertebrate limb.