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# Dynamic modeling of branching morphogenesis of ureteric bud in early kidney development

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ABSTRACT

In the early kidney development, a simple epithelial tube called ureteric bud is derived from the intermediate mesoderm and undergoes a complex process of growth and terminal bifid branching. The branching of the ureteric bud is achieved by different cellular behaviors including cell proliferation and chemotaxis. In this paper, we examine how the branching morphology depends on different physical or chemical factors by constructing a cell-based model to describe the simple tube branching in the early kidney development. We conclude that a proper balance between growth speed of epithelial sheet due to cell proliferation and cell mobility due to chemotaxis is necessary to realize the development of normal Y-shaped pattern. When cell proliferation is fast compared to chemotaxis, kinked pattern is formed, and when cell proliferation is slow, bloated pattern is formed. These are consistent with experimental observations in different morphological anomalies of mutants. We show that the different branching patterns are accurately predicted by growth–chemotaxis ratio.



## 1. Introduction

Branching morphogenesis of epithelial tubules can be seen in the formation of diverse organs in animal development (Cardoso and Lu, 2006; Costantini, 2006; Ghabrial and Krasnow, 2006; Sternlicht et al., 2006; Tucker, 2007). In the early kidney development, a simple epithelial tube called ureteric bud is derived from the intermediate mesoderm and intrudes into metanephric mesenchyme with complex processes of growth and branching (Fig. 1A; Saxen, 1987; Vize et al., 1997; Davies, 2005). The ureteric bud can branch to produce a variety of complex patterns but the most frequently observed is terminal bifid (Al-Awqati and Goldberg, 1998; Majumdar et al., 2003; Watanabe and Costantini, 2004).

Experimental studies have reported that the branching of the ureteric bud is induced by chemotaxis and local cell proliferation at the tip of the ureteric bud. These are triggered by glial cell line-derived neurotrophic factor (GDNF). The source of GDNF is localized at two places in mesenchyme near the tip of the ureteric bud, and the localization is considered as a result of the regulation of *Gdnf* gene expression through epithelium–mesenchyme interaction (Vega et al., 1996; Sariola and Sainio, 1997; Hellmich et al., 1996; Kuure et al., 2000; Majumdar et al., 2003; Sakurai, 2003; Sariola and Saarma, 2003). Since GDNF diffuses within the mesenchymal tissues, its concentration is considered to form a gradient (Sariola and Sainio, 1997; Pohl et al., 2000; Sariola and Saarma, 2003; Michael and Davies, 2004; Shakya et al., 2005). Epithelial cells constituting the ureteric bud climb up along the gradient (Tang et al., 1998, 2002; Kim and Dressler, 2007), and divide in a concentration-dependent manner (Pepicelli et al., 1997; Michael and Davies, 2004) through regulations of different intracellular signaling. The ureteric bud branching can occur without direct contact to mesenchyme but GDNF expressed in mesenchyme is needed for proper branching patterning (Sainio et al., 1997; Qiao et al., 1999; Fisher et al., 2001).

Recent experiments have reported that mutants with the inhibition of cell proliferation or chemotaxis form abnormal patterns of the ureteric bud. The experiments shows that inhibiting cell division at the tips leads to bloated patterns of the ureteric bud, while inhibiting chemotaxis leads to kinked patterns (Fig. 1B; Davies, 2001; Michael and Davies, 2004; Michael et al., 2005; Kim and Dressler, 2007). These morphological abnormalities are likely to be caused by the imbalance between cell proliferation and chemotaxis. However, it is difficult by experiments to know how the morphology of the ureteric bud depends on different cellular behaviors including cell proliferation and chemotaxis in details.

So far, different mechanisms have been proposed to generate branching patterns. For example, Lubkin and Murray (1995) and Lubkin and Li (2002) each modeled the morphology of lung and

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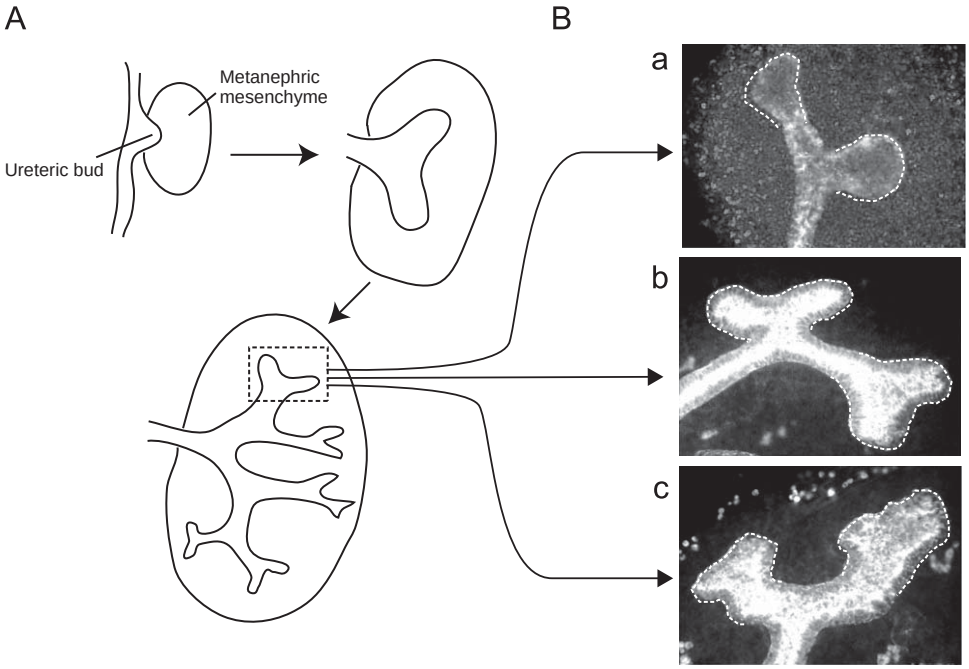


**Fig. 1.** Branching pattern formation in early kidney development. (A) A ureteric bud intrudes into the metanephric mesenchyme and branches within it. Normally, the tip of each branch bifurcates and forms a Y-shaped pattern (B(b)). In the mutant in which cell proliferation is inhibited, a bloated pattern is observed (B(a)), while in which chemotaxis is inhibited, a kinked pattern is observed (B(c)). The figures are reprinted from (a): *Journal of Anatomy*, vol. 204, pp250, Figure 5D, L. Michael and J.A. Davies, 2004 with permission from Wiley Blackwell and Dr. Davies, and (b), (c): *Developmental Biology*, vol. 307, pp295, Figure 5G and H, D. Kim and G.R. Dressler, 2007 with permission from Elsevier, and are minimally modified to serve this study.

salivary gland by the boundary of fluid with different viscosity corresponding to mesenchymal and epithelial tissues. They examined how the boundary shape changes in response to external perturbation or force. Hartmann and Miura (2006) also modeled the lung branching by using diffusion-limited growth, a well-studied branching mechanism in the formation of bacterial colonies (Kawasaki et al., 1997; Mimura et al., 2000; Sugimura et al., 2007). However, few studies explicitly models cellular behaviors such as cell division and chemotaxis as driving forces of branching.

In this paper, we construct a cell-based model including different mechano-chemical factors to describe a ureteric bud formation. For describing organ growth and deformation, we here adopt the cellular Potts model (CPM), which is also called as Glazier–Graner–Hogeweg (GGH) model. In the CPM, each cell is represented as a cluster of connected sites on a regular lattice, and various cellular behaviors such as cell growth, division, apoptosis, chemotaxis, and sorting by heterogeneous adhesivity of cells can be incorporated. Due to the flexible description of tissues, the CPM has been applied to the analyses of diverse morphogenetic processes (Savill and Hogeweg, 1997; Marée and Hogeweg, 2001; Turner and Sherratt, 2002; Zajac et al., 2003; Kiskowski et al., 2004; Merks et al., 2006; Grieneisen et al., 2007; Maeda et al., 2007; Poplawski et al., 2007).

We examine dependence of the branching morphology on different mechano-chemical factors. We find that the morphology can be classified into three major patterns: normal Y-shaped, and abnormal kinked or bloated pattern, and that a major determinant of the morphology is the balance between the cell proliferation rate and the intensity of chemotaxis. To make quantitative discussion possible, we introduce two quantities: (1) integral curvature to characterize the morphology and (2) growth–chemotaxis ratio to quantify the balance between cell proliferation rate and the intensity of chemotaxis. We show that the patterns to be formed are predicted by the growth–chemotaxis ratio very well. Our results are consistent with experimental observations of different morphological anomalies of mutants.

## 2. Model

The cellular Potts model, abbreviated as CPM, represents each cell as a cluster of connected sites on a regular lattice, and traces the behavior of those cells (Graner and Glazier, 1992). In our model, we consider the growth and deformation of one-layer epithelium sheet of the ureteric bud, which separates liquid in the inner duct from mesenchyme outside, as illustrated in Fig. 2. Cells are numbered by $\sigma$ ( $= 1, 2, \ldots, n$), and cell $\sigma$ is adjacent to cell $\sigma$+1 and cell $\sigma-1$.

The state transition of the CPM is performed through the change in the state of a site. This occurs first by randomly choosing a pair of adjacent sites, $\vec{x}$ and $\vec{y}$, which may belong to different cells, or one to a cell and the other to liquid (or mesenchyme). We here consider Moore neighborhood (i.e., each site has eight neighbors, rather than four neighbors in Neumann neighborhood). With some probability (specified below), a state of one site substitute for that of the other site. The net result of such a transition is either the expansion or the shrinking of a cell (or cells). Several physical and biological processes affect the rate of copying. To model these processes, the CPM considers a generalized energy function, named Hamiltonian $H$, and assumes that any candidate of transition is more likely to be realized if the transition would decrease the energy, rather than increase the energy.

To be specific, the state transition in the CPM is performed as follows: first a randomly chosen pair of neighboring sites is selected as a candidate for copying, and the probability for the copying of one site by the other to be realized depends on the