Simulation of the genetic network controlling C. elegans vulval development

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Abstract
The genetic state of a cell is defined by the proteins and other gene products it contains. Changes in the genetic state of a cell result from the interactions between genes that constitute the genetic network. Development consists of such cell state changes. Here we introduce a tool for modelling and simulating the genetic network controlling the development of the C. elegans vulva.

A network derived from the literature was modelled using the Gene-O-Matic software. Known inductive interactions were also incorporated into the model. We present a simulation of the genetic state changes observed during vulval development in wild type and mutant worms.

Introduction
The somatic cell lineage of the nematode Caenorhabditis elegans has been completely determined. The hermaphrodite vulva consists of 22 cells, descending from 3 hypodermal vulval precursor cells (VPCs; see Fig., left).

Genetic studies have led to the identification of hundreds of genes influencing vulval development. Epistasis and biochemical studies have ordered some of these genes into a genetic network.

Our aim is to develop a modelling and simulation tool for testing hypotheses about the molecular and cellular mechanisms of vulval development. For the purpose of illustration, we discuss a simplified vulval genetic network (see Sternberg & Han 1998; Shaye & Greenwald 2002).

Gene-O-Matic
Models of gene networks have tended to concentrate on single cell systems or multicellular treated as one or a few “giant cells”.

We have developed a new software (Gene-O-Matic) that allows the simulation of a gene network in several proliferating, interacting cells. Here we use this software to simulate C. elegans vulval development.

A Gene-O-Matic network is composed of several biological information carriers (BICs). Each BIC can represent a gene or a gene product (e.g., mRNA transcript, active or inactive forms of a protein), depending on the desired level of detail. The signal and strength of the interactions between different BICs are specified in the model. BICs exist in discrete, on/off (Boolean) states.

Simulation
To simulate vulval development, we used approximate cell positions and cell division times from the literature. Cells are simulated in 3D using Cell-O-Sim, and can be visualized in 2D or 3D.

Control of the cell cycle and the cell lineage was incorporated into the genetic network (i.e., it was not hard coded into the simulation).

The software allows us to simulate various experimental manipulations: e.g., cell ablations, null, loss- and gain-of-function mutations, ectopic expression of genes, mosaic analysis.

During a simulation run, the genetic states of the different cells can be recorded for later analysis. Information about the current state of a cell can be obtained at any time. A lineage display, showing the times of cell division and gene activity, is also available.

Results
Here we show simulations of vulval formation in wild type and experimental treatments (Figs. A-C, right), based on a genetic network including the vulval induction and lateral signalling pathways.

The wild type simulation illustrates normal vulva development and begins at ~27h after hatching (L3 stage) with the 6 VPCs (P(3-8); p and the anchor cell (AC).

The AC expresses lin-3 and induces P6.p. This inductive signal is transduced by rrf-23 and activates the let-23/RAS pathway. P6.p then produces a lateral signal to induce P5.p and P7.p through lin-12.

The 3 central VPCs, P(5-7); p, undergo 3 rounds of cell division to generate 22 cells. These adopt 1st and 2nd fates and undergo complex cell movements. The cell bodies also undergo shape modifications and fusions (not shown). The remaining VPCs adopt the nonvulval 3rd fate, dividing once and then fusing with hyp7 (not shown).

In the second simulation (Fig. B) the AC is ablated. This leads to the loss of the inductive signal. Therefore, all VPCs adopt the nonvulval 3rd fate, resulting in a vulval-less phenotype.

The third simulation (Fig. C) consists of the knockout of two repressors of the RAS signalling pathway, lin-15A and lin-15B. This causes all VPCs to adopt vulval fates leading to a multivulval phenotype. Due to the simplicity of our model at V7; C adopt 1st fate, not the alternating 1st and 2nd fates observed in reality.