

Modelling the effect of subcellular mutations on the migration of cells in the colorectal crypt

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Abstract

Background: Many cancers arise from mutations in cells within epithelial tissues. Mutations manifesting at the subcellular level influence the structure and function of the tissue resulting in cancer. Previous work has proposed how cell level properties can lead to mutant cell invasion, but has not incorporated detailed subcellular modelling Results: We present a framework that allows the straightforward integration and simulation of SBML representations of subcellular dynamics within multiscale models of epithelial tissues. This allows us to investigate the effect of mutations in subcellular pathways on the migration of cells within the colorectal crypt. Using multiple models we find that mutations in APC, a key component in the Wnt signalling pathway, can bias neutral drift and can also cause downward invasion of mutant cells in the crypt. Conclusions: Our framework allows us to investigate how subcellular mutations, i.e. knockouts and knockdowns, affect cell-level properties and the resultant migration of cells within epithelial tissues. In the context of the colorectal crypt, we see that mutations in APC can lead directly to mutant cell invasion.

Full-text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.

Figures

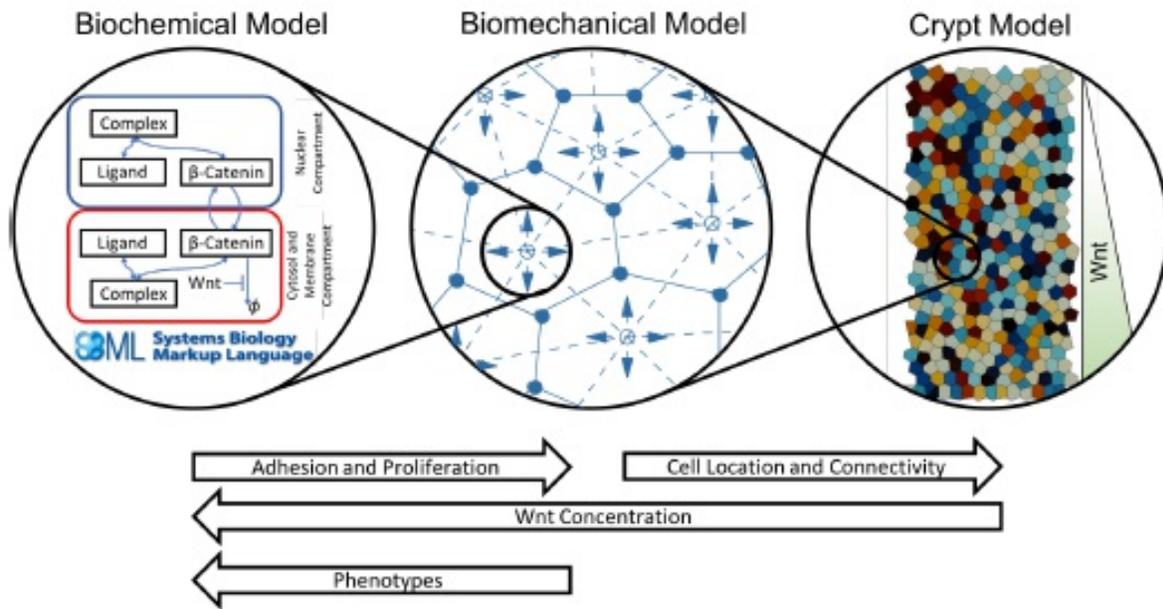
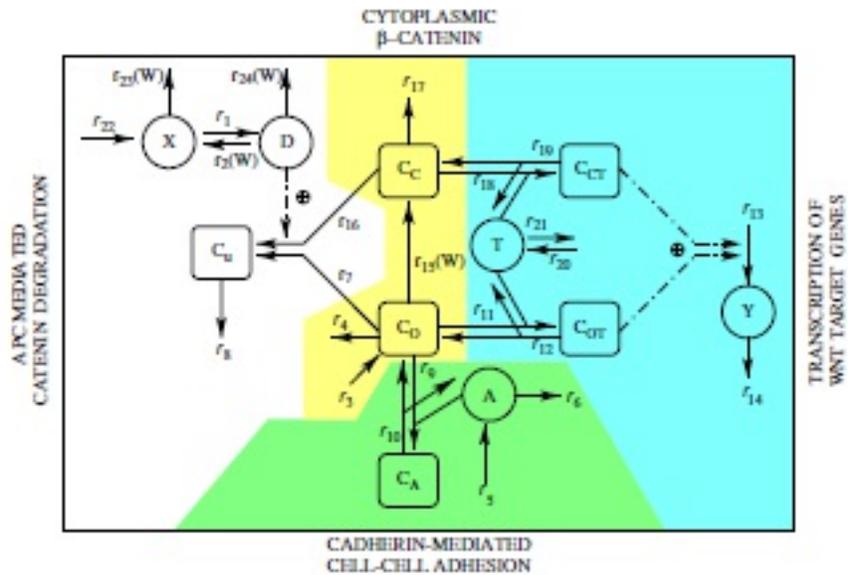
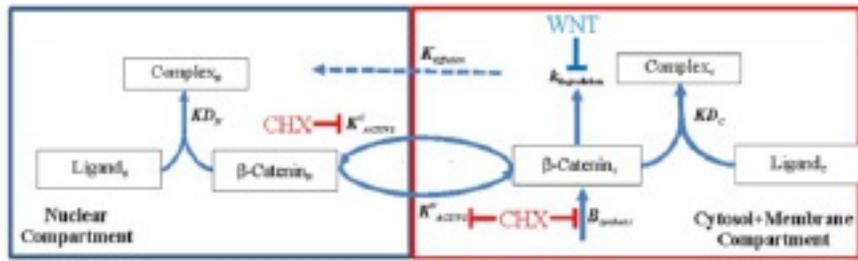


Figure 1

Schematic of the Model. The crypt model comprises a biomechanical model (the voronoi tessellation model found in Chaste) and a suitable biochemical model specified in SBML. The biochemical model specifies adhesion and cell proliferation in the biomechanical model which leads to cell movement in the crypt model. Cell phenotype (mutation level) and Wnt concentration are provided to the biochemical model by the biomechanical and crypt models respectively. SBML logo reproduced with permission from <http://www.sbml.org>.



(a) VL



(b) Tan

Figure 2

Subcellular model schematics. a) Schematic representation of the VL model, which describes the dynamics of active destruction complexes (D), axin molecules (X), adhesion molecules (A), transcription molecules (T), Wnt target proteins (Y) and six pools of β -catenin (C_i , $i = A, c, cT, o, oT$ and u). Reproduced with permission from [32]. b) Schematic representation of the Tan model which describes the dynamics of free and bound β -catenin in the cytosol-membrane (BC, NC) and nucleus (BN, NN), and free ligands in the cytosol-membrane (LC) and nucleus (LN). Reproduced with permission from [46].

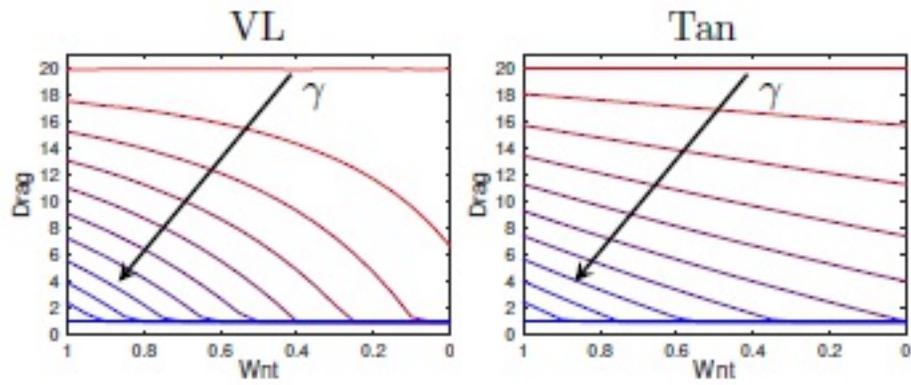


Figure 3

Drag functions: Drag as a function of the level of complex in the cytosol/membrane (CA in the VL model and NC in the Tan model). The lower, the higher the drag. I.e. for mutant cells the amount of complex in the cytosol/membrane increases, as seen in Figure 8, and we assume that this increases the drag. Also when the Wnt signal is higher, the drag will be higher for $\gamma = 0$ (as the amount of complex is higher). Arrows are drawn in the direction of increasing. The cases are shown for $\gamma = 0 \square 1$ in increments of 0.1 ($\gamma = 0$ is red, $\gamma = 1$ is blue).

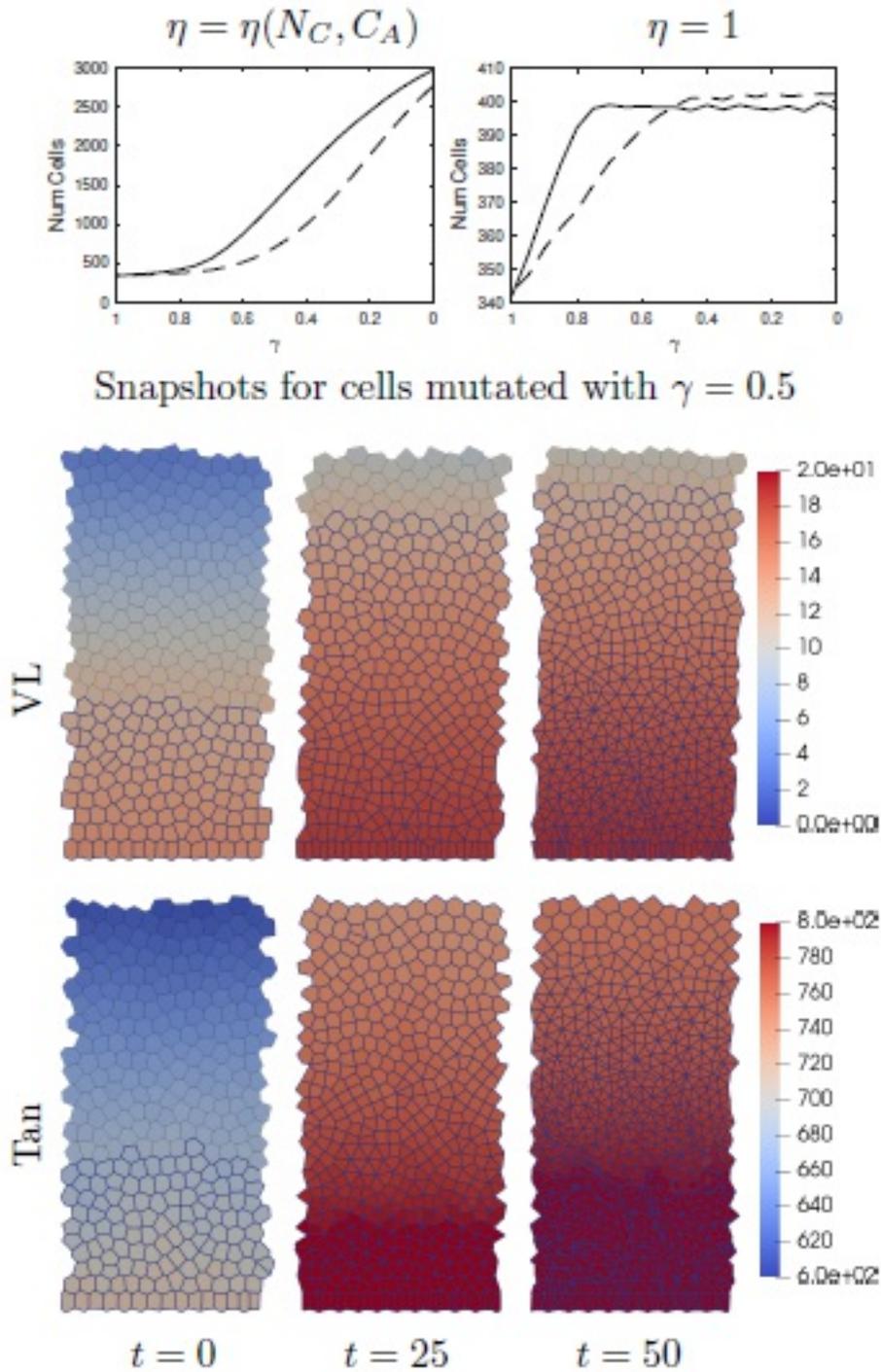
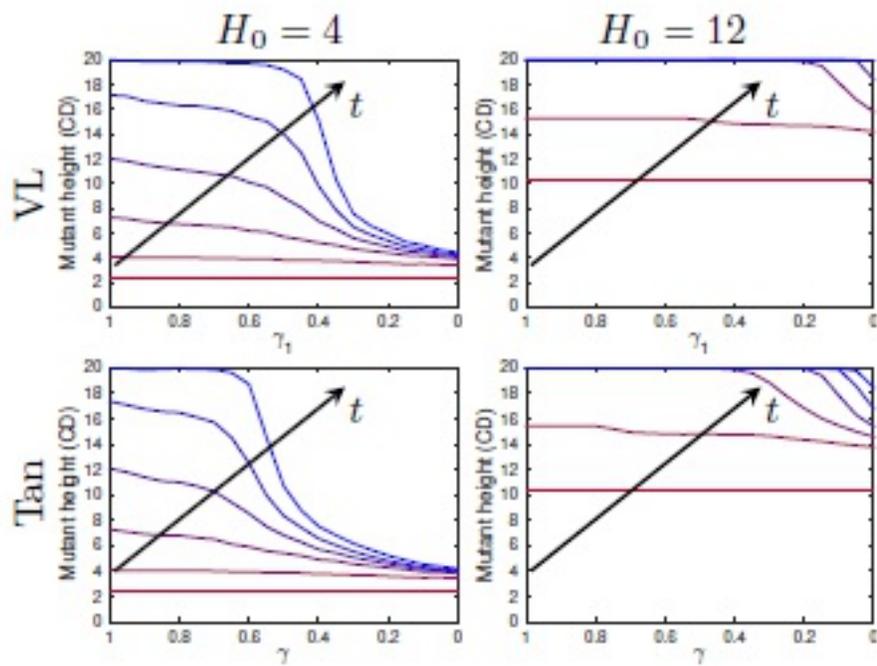


Figure 4

Number of cells in the crypt as a function of mutation parameter. Top) Averaged over 100 simulations for constant ($\eta = 1$) and variable drag (Equation (3)). All cells are mutated in a dynamic equilibrium, at time $t = 0$, the number of cells are counted at $t = 50$ hours. Dashed lines are with the VL model and solid line are with the Tan model. Bottom) Snapshots of

simulations using the adhesion complex dependent drag functions defined in Equation (3). (random seed = 0). Proliferative cells are outlined in blue and cell color indicates level of nuclear complex. All cells in the crypts are mutated at time $t = 0h$, with parameter = 0:5, for both models.



Mutation patch $\gamma = 0.25$ and $H_0 = 4$

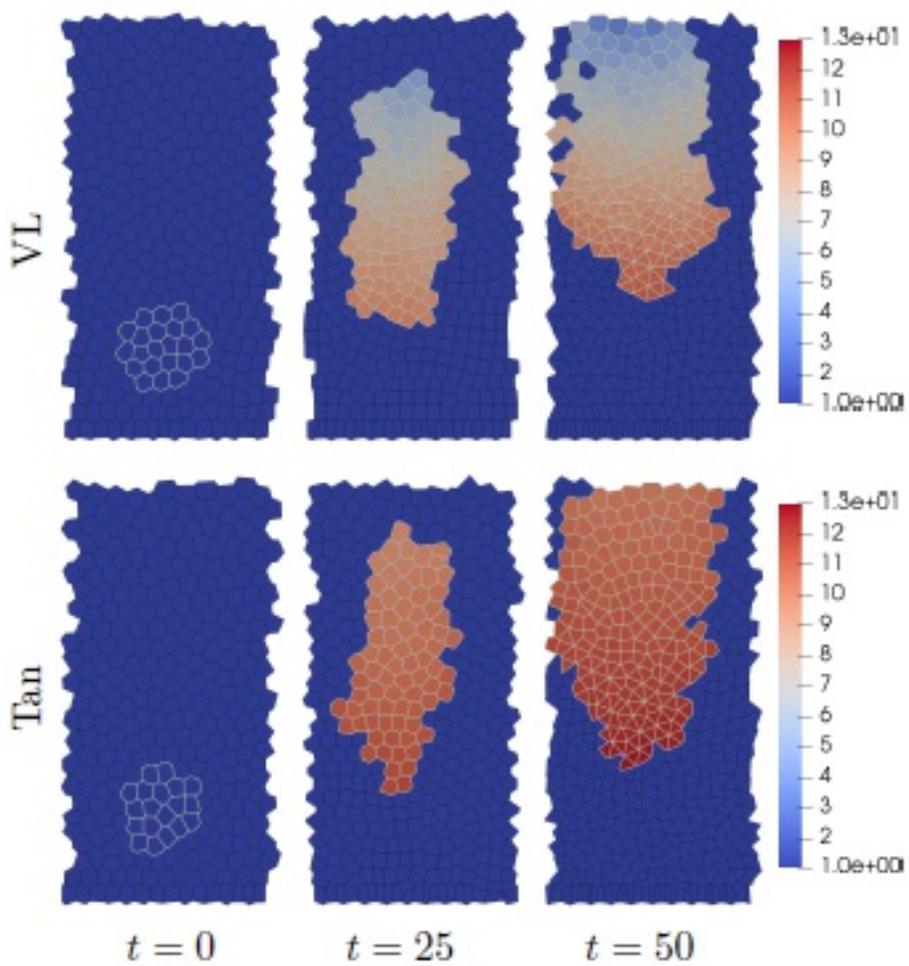
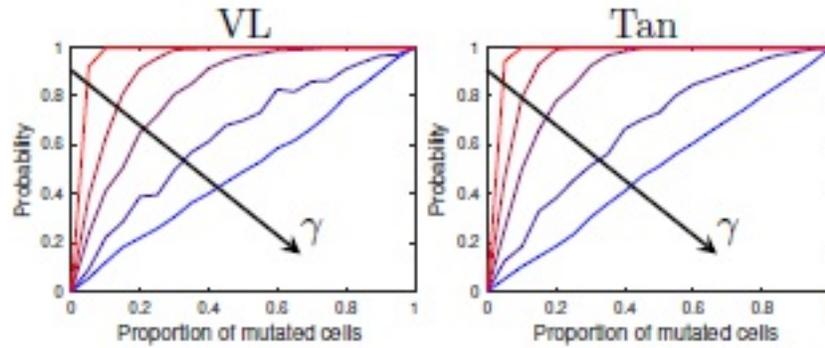


Figure 5

Mutant cells remain in the crypt due to increased adhesion and proliferation. Top) Mutant height plotted at times $t = 0, 10, 20, 30, 40, 50$ h after mutating cell. The simulations start with a mutant patch of radius 2, and initial centre height H_0 . The mutant height is given in cell diameters. Bottom) Snapshots of simulations with mutant cells at bottom of crypt, $H_0 = 4$. (random seed =0). Mutated cells are outlined in grey and the cell color indicates level of drag coefficient, μ , applied to the cell (function of adhesion complex). Mutant cells in the crypts are mutated at time $t = 0$ h, with parameter = 0:25, for both models.



Mutation takeover $\gamma = 0.9$ and $p_{\text{Mutated}} = 0.5$

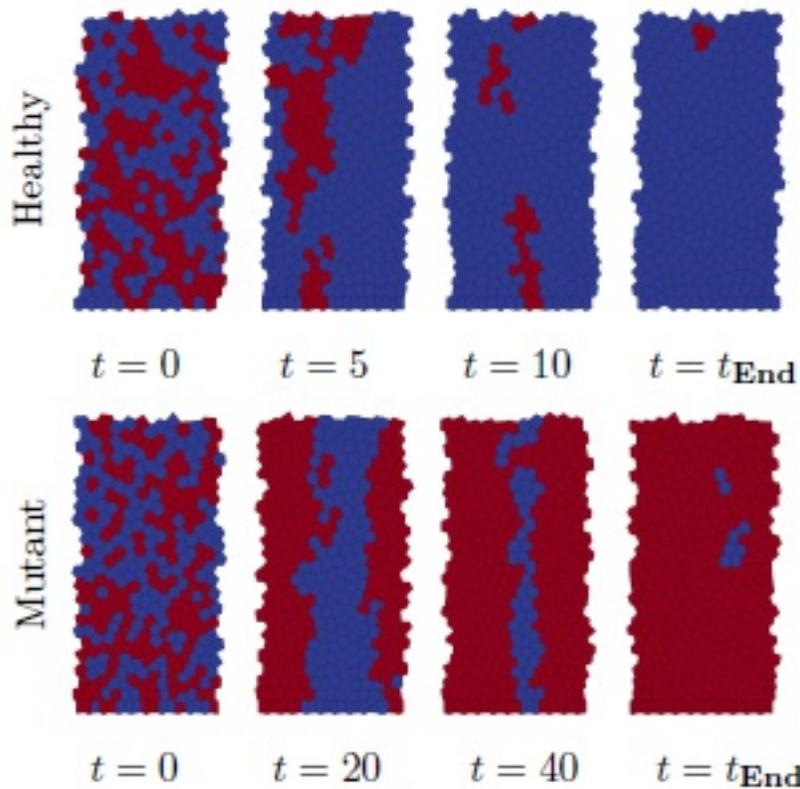


Figure 6

Mutant cells invade the crypt. Top) probability of mutant cells taking over the crypt as a function of initial proportion of mutated cells, for the VL and Tan models as the mutation parameter is varied. results are presented for $\gamma = 0$ (red); 0.5; 0.75; 0.9; and 1 (blue) and the arrow is in the direction of increasing γ . Bottom) Snapshots of 2 simulations with 50% mutated cells. In the top simulation healthy cells happen to out compete the mutant cells, in the bottom simulation mutant cells win. Note, specific simulations were chosen to illustrate the conversion to homogeneous crypts.

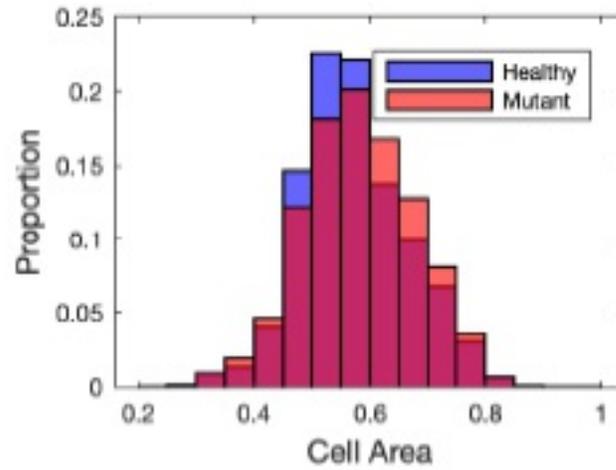


Figure 7

Mutant cells maintain cell volume in homogeneous crypts. Distribution of healthy and mutant cell areas for heterogeneous crypts from Figure 6 using the Tan model for cell signalling. Cell age is measured after 20 hours within 100 crypts initially comprised of an equal quantity of healthy ($= 1$) and mutated cells ($= 0.5$). The mean healthy cell area is

0.5725 CD2, and the mean mutant cell area is 0.5826 CD2.

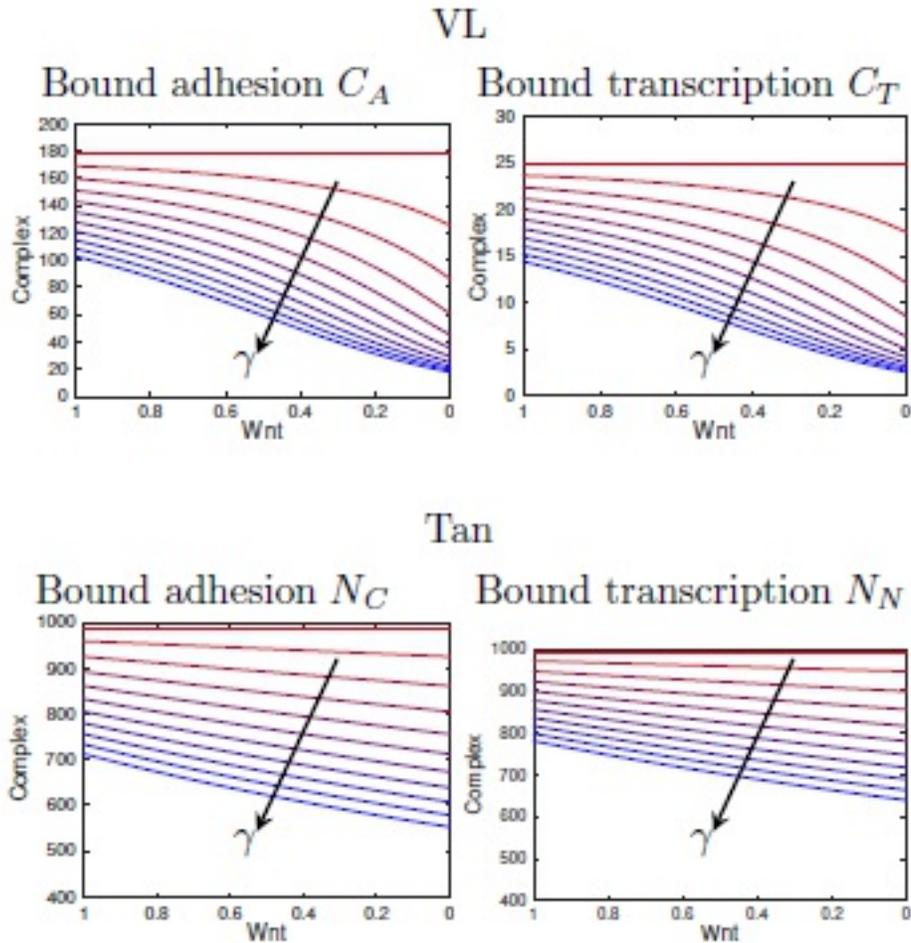


Figure 8

The effect of varying the expression of the APC mutation parameter, γ , on the bound complexes in the nucleus and cytosol-membrane. For the VL (top) and Tan models (bottom). Arrows are drawn in the direction of increasing γ . Decreasing γ increases the amount of bound complexes in both the complexes for adhesion and transcription. The cases are shown for $\gamma =$

$0 \leq \gamma \leq 1$ in increments of 0.1 ($\gamma = 0$ is red, $\gamma = 1$ is blue).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMovie2.mp4
- SupplementaryMovie1.mp4
- SI Figure 1.jpg
- Tan2014Sbml.xml
- VanLeeuwen2007Sbml.xml
- SupplementaryMovie3.mp4

