A hybrid approach to multiscale modelling of cancer: Supplementary material

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Supplementary material I: Simulation results from continuum model

As explained in Sec. 2(b), we use the continuum model to simulate the evolution of a patch of mutant cells on the wall of a crypt. The surrounding normal cells proliferate in the lower third of the crypt. Their expansion drives an upward flow of both normal and mutant cells towards the top of the crypt. The mutant cells proliferate at a uniform rate, so that the initially circular patch grows and changes shape. Different levels of adhesion between normal or mutant cells and the underlying stroma are illustrated in Figures 1-3, which show evolving patch shapes and velocity and pressure fields for mutant cells with low ($\phi_M < 1$) and high ($\phi_M > 1$) levels of adhesion relative to the normal cells. When the mutant cells have low adhesion, there is only a small pressure difference across the patch (Figure 3(a)) and the patch rises rapidly (Figure 2(a)), expanding as it does so. The rising patch displaces surrounding normal cells rather like a buoyant bubble (Figure 2(a)). As ϕ_M increases the rise speed falls (Figure 1) and a large pressure difference is generated across the patch (Figure 3(b)); now normal cells are forced to flow sideways around the slowly moving patch (Figure 2(b)). Ultimately the patch of mutant cells is predicted to expand non-uniformly into a tear-drop shape (Figure 1), reflecting the vertical pressure gradient in the surrounding normal cells

Significantly, if the mutant cells are sufficiently adherent to the stroma and proliferate sufficiently rapidly, it is possible for the mutant patch to expand downwards as well as upwards (Figure 7(d)). The model therefore captures both "bottom-up" and "top-down" invasion. Bottom-down invasion requires the patch to grow from a location sufficiently close to the base of the crypt, as shown in Figure 8(c,f).

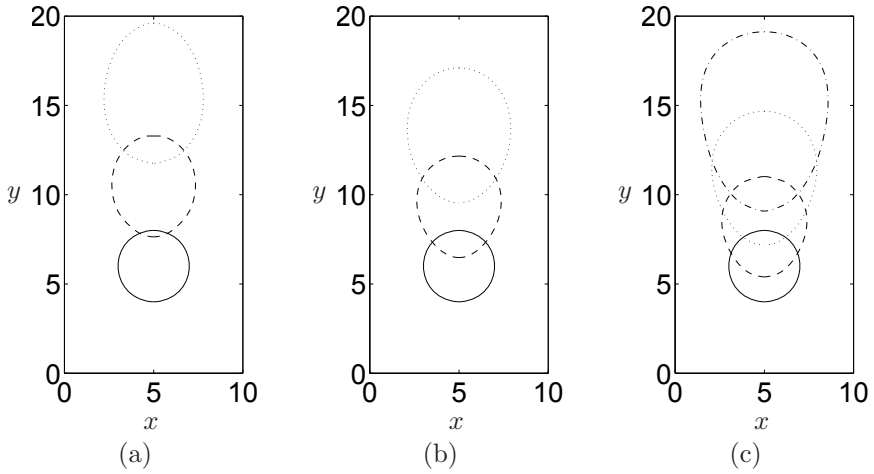

Figure 1: Series of plots showing how the pattern of invasion of an initially circular patch of mutant cells spreads within a crypt as their relative viscosity, ϕ_M, varies. If the mutant cells are less viscous than the normal cells ($\phi_M < 1$) then the mutant cells are forced out of the crypt by the proliferative force exerted on them by normal cells below them. If $\phi_M > 1$ then the mutant cells offer more resistance to movement and force the proliferating cells to move around the growing patch, enabling them to spread downwards into the crypt. In each simulation, the location of the interface separating the mutant and normal cells is plotted at times $t = 0$ (solid line), $t = 8$ (dashed line) and $t = 16$ (dotted line), $t = 24$ hours (dot-dash line). Parameter values: $k = 1.0$ and (a) $\phi_M = 0.5$, (b) $\phi_M = 1.0$, (c) $\phi_M = 2.0$.

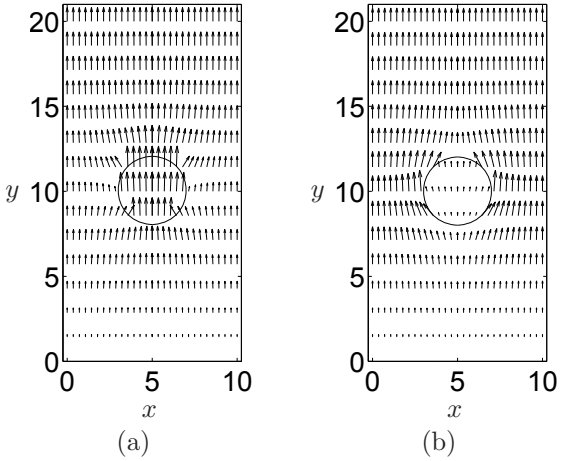

Figure 2: Plots showing how the velocity field varies for two different values of ϕ_M, with $k = 1$. When $\phi_M = 0.2$ (a), the mutant cells are less viscous than the surrounding normal cells which move towards the patch and force it up the crypt. When $\phi_M = 5.0$ (b), the mutant cells are more viscous than the normal cells which move around the patch.

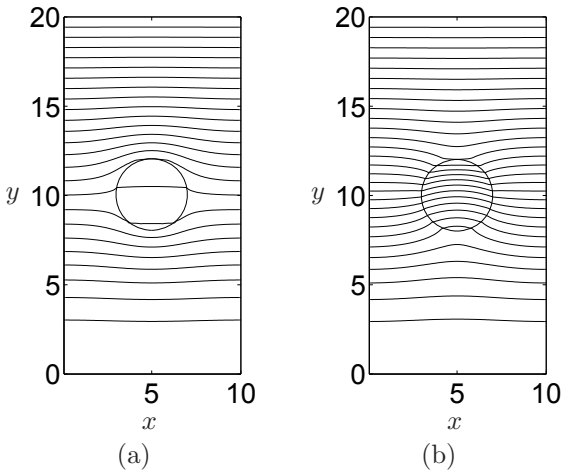

Figure 3: Plots of the pressure contours within the crypt for the simulations presented in figure 2, showing high pressure at the crypt base and zero pressure at the top. When the mutant cells are less viscous than the normal cells ($\phi_M = 0.2$), forces transfer more readily through the patch than through the normal cells leading to a lower pressure near its base. When the mutant cells are more viscous ($\phi_M = 5.0$), forces transfer less easily through the patch, leading to a higher pressure near its base. The contours are placed every 0.3 units of pressure, with $\hat{p} = 0$ at $y = 1$ and $p = 7.0$ in (a) and $p = 7.5$ in (b) at $y = 0$.

Supplementary material II: Table of parameters for the cell-based models

Parameters common to all models				
H_C	-	Crypt height ([cell diameters])	-	20
W_C	-	Crypt width ([cell diameters])	-	10
H_W	-	Proliferative region ([cell diameters])	-	20/3
t_{cc}	-	$G_1 + S + G_2 + M$ time (hours)	-	$\mathcal{N}(16.0, 0.5)$
Parameters specific to the cell-centre model				
k_{ij}	-	Spring strength (Kg hours^{-2})	-	85
s_{ij}	-	Mature cell spring rest length ([cell diameters])	-	1.0
μ_N	-	Cell drag for healthy cells (Kg hours^{-1})	-	1.0
μ_M	-	Cell drag for mutant cells (Kg hours^{-1})	-	varies
Parameters specific to the cell-vertex model				
γ_N	-	Cell-cell adhesion (Kg hours^{-2}[cell diameters])	-	1
γ_B	-	Cell-boundary adhesion (Kg hours^{-2}[cell diameters])	-	1
A_T	-	Mature natural cell area ([cell diameters]^2)	-	$\pi/4$
C_T	-	Mature natural cell perimeter ([cell diameters])	-	π
λ	-	Cell-size constraint (Kg hours^{-2}[cell diameters]$^{-2}$)	-	100
β	-	Cell-perimeter constraint (Kg hours^{-2})	-	10
η_N	-	Cell drag for healthy cells (Kg hours^{-1})	-	1
η_M	-	Cell drag for mutant cells (Kg hours^{-1})	-	varies

Table 1: Parameter values used in the different cell-level models.