Supplementary Table 1. *List of model assumptions*

Model assumption	**Reference**
The shape and ratios of cells in the starting geometry; a prostatic acinus	(1)
The prostatic acinus is surrounded by ECM	(2)
ECM has variable permeability, depending on the stage of the disease	(2)
The presence and percentage of prostate cancer stem cells	(3,4)
Tissue resident fibroblasts are quiescent and become active upon receiving a signal	(5)
Basement membrane is quiescent and functions as a barrier between the inside and outside of the acinus.	(1,6)
Quiescent cells remain in equilibrium/homeostasis; they do not migrate, proliferate or die	Trivial
Basement membrane is broken down by proteolytic enzymes produced by tumor cells. Not all enzyme production results in actual break down (only 10-30 percent)	(6)
Basement membrane break down does not happen right away, so tumor cells have to gain a certain amount of mutations before they can start break down	(6)
Basal cells and non-mutated luminal cells are in homeostasis; they can die and proliferate at low rates, within their normal/healthy regions	Trivial
Basal cells should always be attached to the basement membrane	(6)
Basal cells can only die after enough luminal cells have mutated	(7)
Non-quiescent cells can spontaneously enter apoptosis and die	(8), Experiments
Luminal cells can gain mutations	(1)
Mutated luminal cells have a higher chance of gaining another mutation and are not quiescent or in equilibrium	(1)
Luminal stem cells can also gain mutations, generating ’cancer stem cells’	(1)
Mutated cells can proliferate	Experiments
Upon gaining a mutation, oncogenic or tumor suppressing genes are affected. Mutated cells gain a proliferative advantage	(9)
Apart from the ’standard’ actions proliferate,migrate and die, mutated cells can perform additional actions (parallel to the other actions) once they have gained enough mutations	Trivial
Additional actions of mutated cells include: affecting differentiation of macrophages, breaking down basement membrane and affecting ECM permeability	(2,6,10)

Mutated cells can only break down basement membrane if they are directly adjacent to it	Assumption
Mutated cells move by a random walk and migrate towards fibroblasts	Experiments, (11)
Activation of tissue resident fibroblasts happens during PIN and is affected by mutated cells. CAFs co-evolve during disease progression.	(12–15)
The effect of CAFs on tumor cells depends on the distance between the two	(16)
CAFs can migrate towards mutated cells	(8)
CAFs can proliferate and migrate more than normal fibroblasts	(5)
CAFs stimulate primary tumor growth	(17)
CAFs elicit Epithelial Mesenchymal Transition (EMT) in mutated cells	(18)
CAFs modify the ECM; making it rather impermeable at the beginning and produce MMPs later on to degrade it	(2,13,19)
Macrophages cannot proliferate (the few times they possibly could does not affect simulations)	Experiments
M1 macrophages enter the simulation from one point, mimicking entry via a blood vessel	(20)
Macrophages migrate towards mutated cells, but only if they are in reach (17 grid spaces). If they are further away, they move randomly	(8,19)
Macrophages infiltrate prostatic acini during PIN	(21,22)
Macrophages can kill mutated cells. M1 polarized macrophages are more likely to kill than M2 polarized macrophages	Experiments, (23)
If a macrophage kills a mutated cell, more macrophages are drawn to the acinus (increased influx)	(21,22)
M2 macrophages do not enter the simulation via the blood, but have to arise from differentiation of the M1 macrophages	(20)
M2 polarized macrophages promote mutated cell proliferation	Experiments, (20,21)
Macrophages have to be adjacent to mutated cells to be able to promote those or kill those	(21,24)
M2 macrophages can elicit anchorage independent growth in tumor cells	(21,25)

Supplementary Table 1. Assumptions that were made during model development, including their source.

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