# Population and evolutionary dynamics of tumour growth

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# Outline

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# Population-dynamical aspects of tumour growth[2]

1. Cancer is a disease of clonal evolution within the body[1]

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3. The succession of somatic mutations to which cancer cells are subjected leads to clonal expansion and heterogeneity
4. Heterogeneity is a key aspect since it almost directly leads to drug resistance

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# Effects on targeted cance therapy[3]

## Evolutionary dynamics of cancer poses a barrier to targeted therapy efficiency

### Evolutionary dynamics of carcinogenesis and why targeted therapy does not work

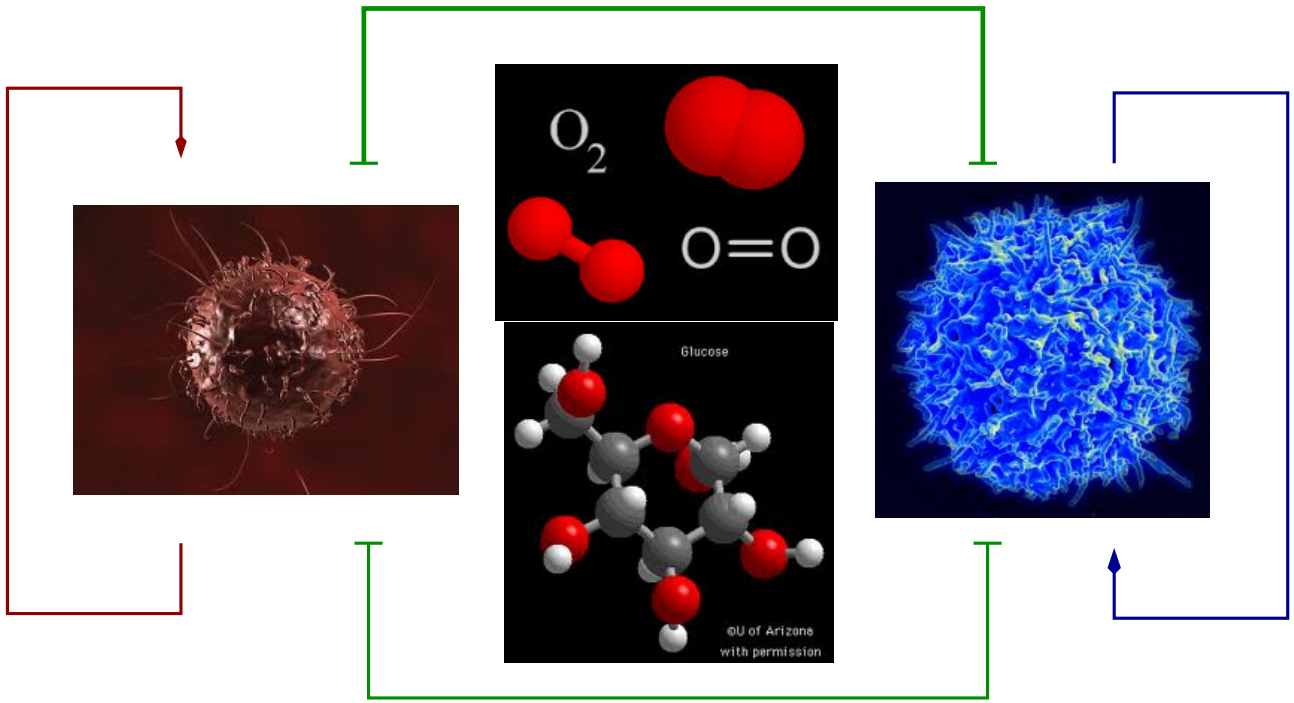
*Robert J. Gillies, Daniel Verduzco and Robert A. Gatenby*

Abstract | All malignant cancers, whether inherited or sporadic, are fundamentally governed by Darwinian dynamics. The process of carcinogenesis requires genetic instability and highly selective local microenvironments, the combination of which promotes somatic evolution. These microenvironmental forces, specifically hypoxia, acidosis and reactive oxygen species, are not only highly selective, but are also able to induce genetic instability. As a result, malignant cancers are dynamically evolving clades of cells living in distinct microhabitats that almost certainly ensure the emergence of therapy-resistant populations. Cytotoxic cancer therapies also impose intense evolutionary selection pressures on the surviving cells and thus increase the evolutionary rate. Importantly, the principles of Darwinian dynamics also embody fundamental principles that can illuminate strategies for the successful management of cancer.

[3] Gillies, Verduzco & Gatenby. Nature Rev. Cancer (2012)

# Cancer as an evolutionary ecology problem

## Competition between normal and cancer cells



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  - Vascularised metastases that are held at an equilibrium size by the immune system

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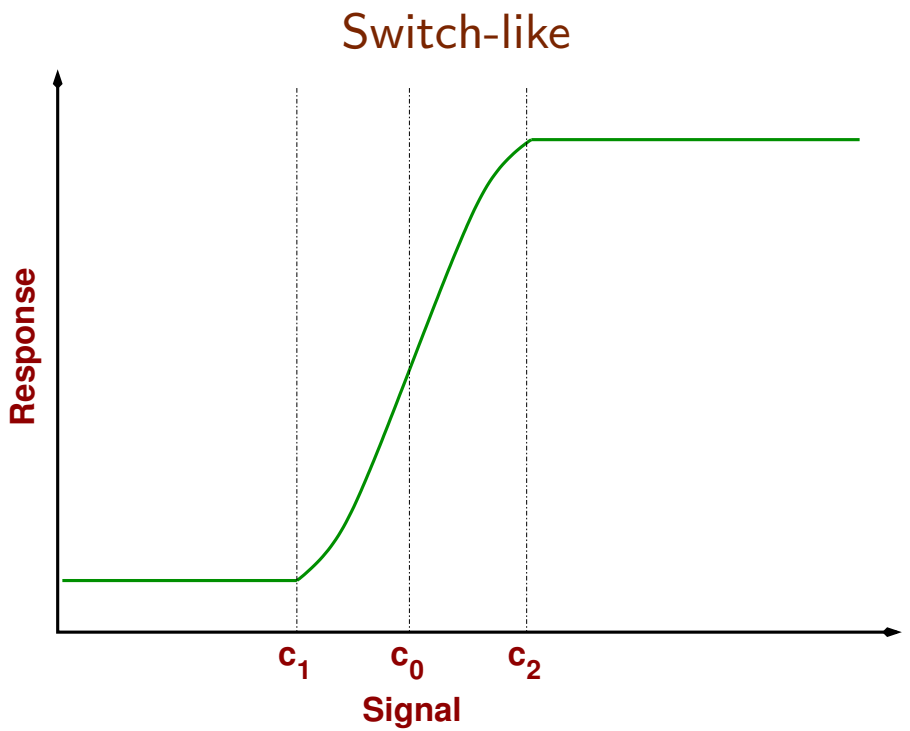
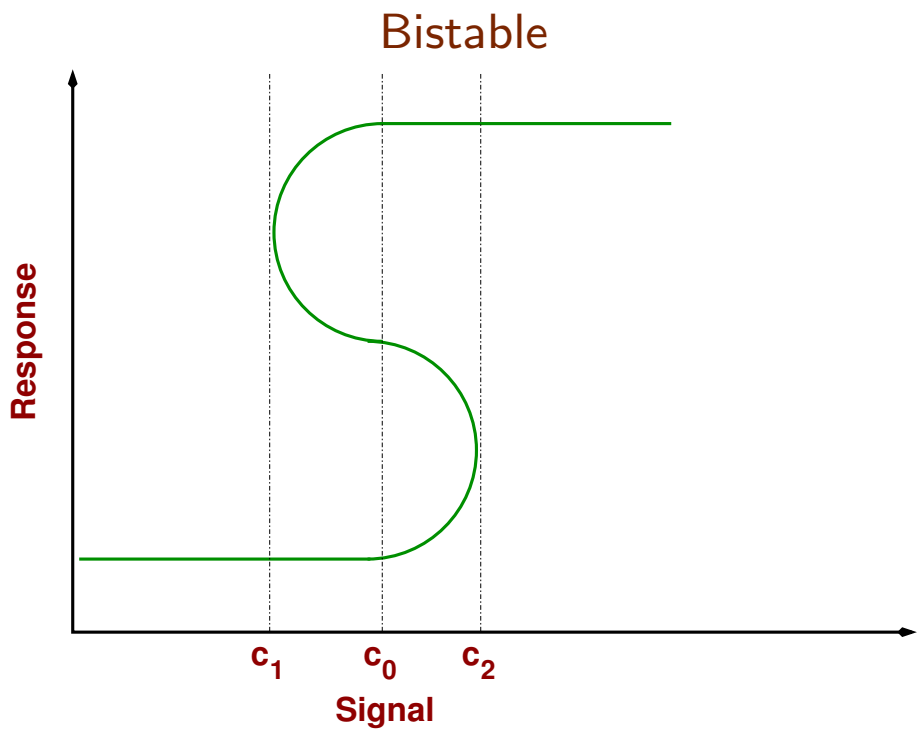
# Outline

# Two strategies to use up available resources

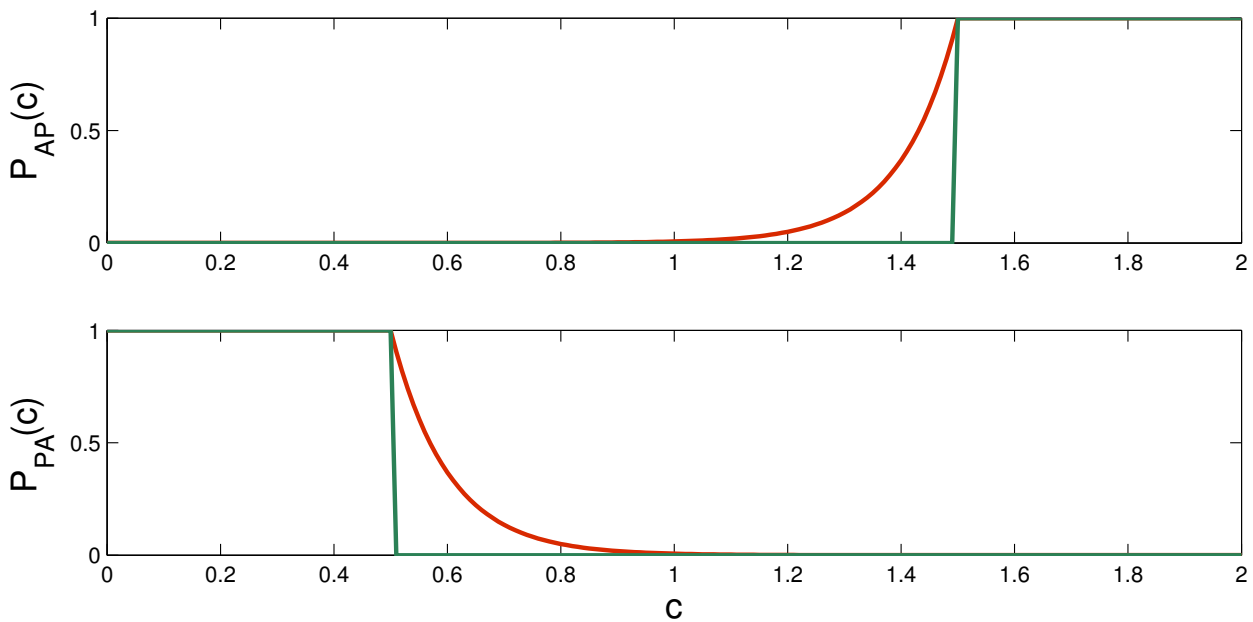
## Switch-like vs Bistable Response Curves



# Two cellular populations

- Switch-like cells.
  1. Birth probability $\begin{cases} \sim 1 \text{ when } c > c_2 \\ \sim 1/2 \text{ when } c \simeq c_0 \\ \sim 0 \text{ when } c < c_1 \end{cases}$ . Death probability $\begin{cases} \sim 0 \text{ when } c > c_2 \\ \sim 1/2 \text{ when } c \simeq c_0 \\ \sim 1 \text{ when } c < c_1 \end{cases}$
- Bistable cells.
  1. Two phenotypes: Proliferating and Quiescent
  2. Proliferating cells duplicate or change phenotype to quiescent
  3. Quiescent cells die or change phenotype to proliferating
  4. The dynamics of the population is then controlled by the rates at which cells switch phenotype:



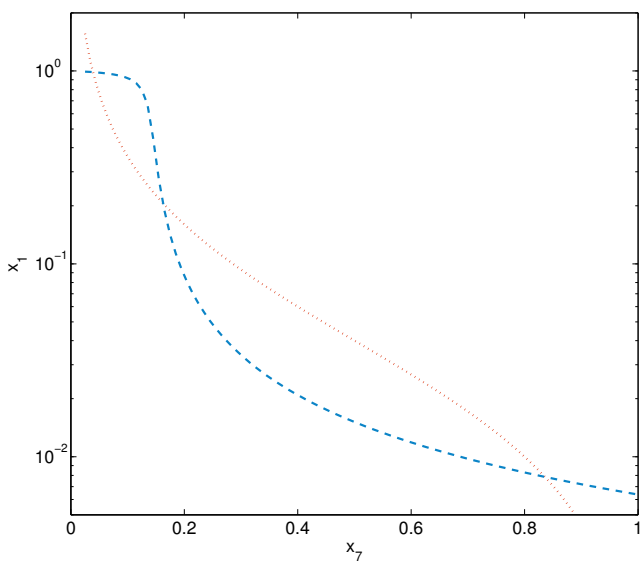
# Example: Model for the cell-cycle

## Simple model for the $G_1/S$ transition

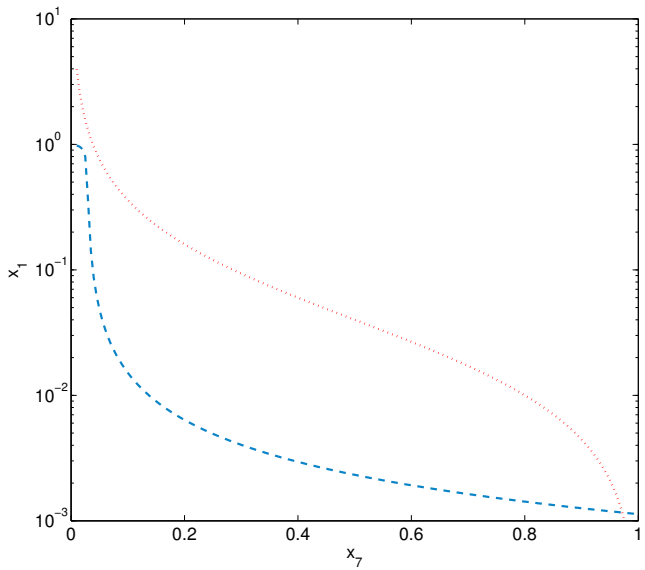
- $x_1$ =[Cdh1], $x_7$ =[CycB/Cdk1], $m$ = cell mass

$$\frac{dx_1}{dt} = \frac{(k_{31} + k_{32}A)(1 - x_1)}{J_3 + 1 - x_1} - \frac{k_4 m x_7 x_1}{J_4 + x_1},$$
$$\frac{dx_7}{dt} = k_1 - (k_{21} + k_{22}x_1)x_7$$

$m = 0.2$




$m = 1$



# Population dynamics

The system we are considering is the competition between an incumbent population of switch-like cells and an invasor made out of bistable cells. These two populations compete by a shared resource, eg oxygen.

## Oxygen concentration

$$\frac{\partial c}{\partial \tau} = \nabla^2 c - \kappa c \sum_{k=1}^{N_T} \chi^{(k)}, \quad \left.\frac{\partial c}{\partial x}\right|_{x=0} = h_0, \quad \left.\frac{\partial c}{\partial x}\right|_{x=L} = -h_L \tag{1}$$

with $h_0 - h_L = Lh^{-1}\bar{\kappa}\Omega c_0$. The parameter $\Omega$ corresponds to the total cell population that a uniform concentration of oxygen $c(x,t) = c_0$ is capable of sustaining. $\chi^{(k)}$ is the population vector corresponding to the $k$th cellular type $k = 1, \ldots, N_T$. $N_T = 3$: Switch-like cells, proliferating bistable cells, and quiescent bistable cells.

# Population dynamics (cont.)

## Master Equation for the cellular populations

$$\begin{aligned}\frac{\partial P(\chi^{(1)},\ldots,\chi^{(N_T)},t)}{\partial t} = & \sum_{k=1}^{N_T}\sum_{i=1}^{N}\left(\mathcal{E}^{-}_{\chi_i^{(k)}}-1\right)T_{\chi_i^{(k)}+1|\chi_i^{(k)}}P+\left(\mathcal{E}^{+}_{\chi_i^{(k)}}-1\right)T_{\chi_i^{(k)}-1|\chi_i^{(k)}}P \\ & \sum_{k=1}^{N_T}\sum_{i=1}^{N}\sum_{j\neq k}\left[\left(\mathcal{E}^{-}_{\chi_i^{(k)}}\mathcal{E}^{+}_{\chi_i^{(j)}}-1\right)T_{\chi_i^{(k)}+1\chi_i^{(j)}-1|\chi_i^{(k)}\chi_i^{(j)}}P+\right. \\ & \left.\left(\mathcal{E}^{+}_{\chi_i^{(k)}}\mathcal{E}^{-}_{\chi_i^{(j)}}-1\right)T_{\chi_i^{(k)}-1\chi_i^{(j)}+1|\chi_i^{(k)}\chi_i^{(j)}}P\right]+ \\ & \sum_{k=1}^{N_T}\sum_{i=1}^{N}\sum_{j\in\langle i\rangle}\left[\left(\mathcal{E}^{-}_{\chi_i^{(k)}}\mathcal{E}^{+}_{\chi_j^{(k)}}-1\right)T_{\chi_i^{(k)}+1\chi_j^{(k)}-1|\chi_i^{(k)}\chi_j^{(k)}}P+\right. \\ & \left.\left(\mathcal{E}^{+}_{\chi_i^{(k)}}\mathcal{E}^{-}_{\chi_j^{(k)}}-1\right)T_{\chi_i^{(k)}-1\chi_j^{(k)}+1|\chi_i^{(k)}\chi_j^{(k)}}P\right]\end{aligned}$$

where $\chi^{(k)}$ is the population vector corresponding to the $k$th cellular type $k=1,\ldots,N_T$ and $\mathcal{E}^{\pm}_{\chi_i^{(k)}}f(\chi_i^{(k)})=f(\chi_i^{(k)}\pm 1)$.

# Population dynamics (cont.)

## Dimensionless transition rates

| Transition rate | Event |
|---|---|
| $T_{\chi_i^{(1)}+1\|\chi_i^{(1)}} = \epsilon \frac{e^{\alpha_0(c-1)}}{e^{\alpha_0(c-1)}+e^{-\alpha_0(c-1)}} \chi_i^{(1)}$ | Switch-like cell division |
| $T_{\chi_i^{(1)}-1\|\chi_i^{(1)}} = \epsilon \frac{e^{-\alpha_0(c-1)}}{e^{\alpha_0(c-1)}+e^{-\alpha_0(c-1)}} \chi_i^{(1)}$ | Switch-like cell death |
| $T_{\chi_i^{(2)}+1\|\chi_i^{(2)}} = \epsilon \chi_i^{(2)}$ | Bistable proliferating cell division |
| $T_{\chi_i^{(3)}+1\chi_i^{(2)}-1\|\chi_i^{(3)}\chi_i^{(2)}} = \epsilon w_0 e^{-H_{PA}(c)} \chi_i^{(2)}$ | Proliferating-to-quiescent switch |
| $T_{\chi_i^{(2)}+1\chi_i^{(3)}-1\|\chi_i^{(2)}\chi_i^{(3)}} = \epsilon w_0 e^{-H_{AP}(c)} \chi_i^{(3)}$ | Quiescent-to-proliferating switch |
| $T_{\chi_i^{(3)}-1\|\chi_i^{(3)}} = \epsilon \chi_i^{(3)}$ | Bistable quiescent cell death |
| $T_{\chi_i^{(k)}-1\chi_j^{(k)}+1\|\chi_i^{(k)}\chi_j^{(k)}} = \epsilon \nu_k \chi_i^{(k)}$ | Cell migration $\forall\, k$ and $\forall\, j \in < i >$ |

Table : Dimensionless transition rates for our stochastic model of competition between switch-like and bistable populations.

# Aims

- Examine the effect of intracellular noise on the long-term behaviour of the competition between sitch-like and bistable populations
- Explore intracellular noise as a mechanism for latency (i.e. long-term survival of a non-invading mutant)
- Analyse the role of cell motility
- Study the therapeutic implications of our model

# Outline

# Low-noise behaviour: Invasion in well-stirred systems

## Hybrid Gillespie simulation results

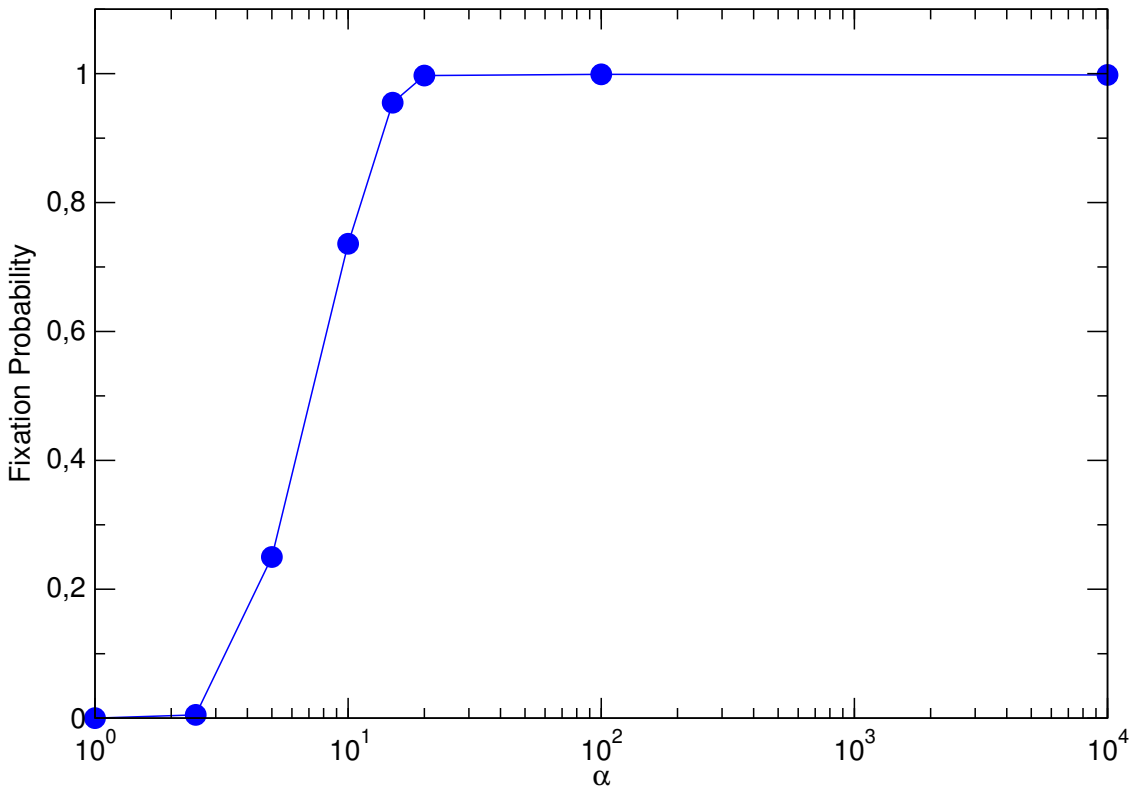
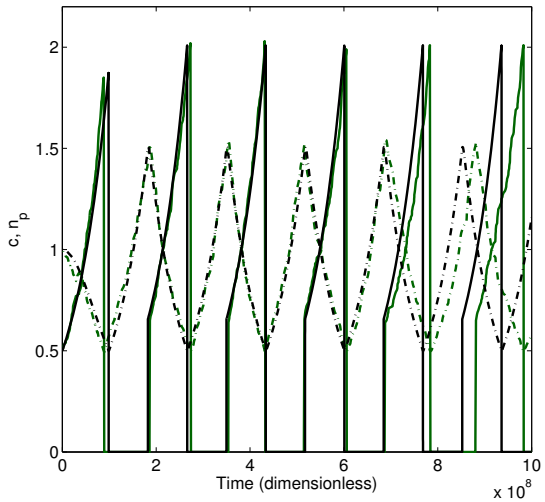



Figure : Simulation results for the fixation probability of the mutant (bistable) cell population as a function of the barrier-to-noise ratio $\alpha$. The initial mutant-to-incumbent ratio $y = 1/500$. $w_0 = 10^2$.

# Supression of intracellular noise reduces population noise

## Comparison between Gillespie simulations and the mean-field approximation

$\Omega = 100$

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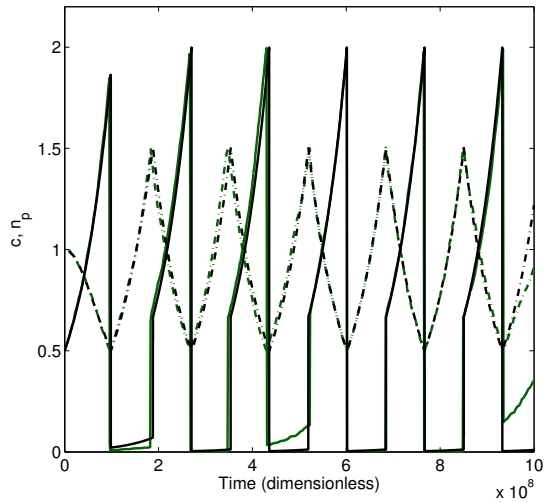



$$\frac{dc}{d\tau} = \kappa\Omega - \kappa\left(n_s + n_p + n_q\right)c \tag{3}$$

$$\frac{dn_s}{d\tau} = \epsilon \tanh\left(\alpha_0(c-1)\right) n_s \tag{4}$$

$$\frac{dn_p}{d\tau} = \epsilon n_p - \epsilon w_0 P_{PA}(c) n_p + \epsilon w_0 P_{AP}(c) n_q \tag{5}$$

$$\frac{dn_q}{d\tau} = -\epsilon n_q + \epsilon w_0 P_{PA}(c) n_p - \epsilon w_0 P_{AP}(c) n_q \tag{6}$$

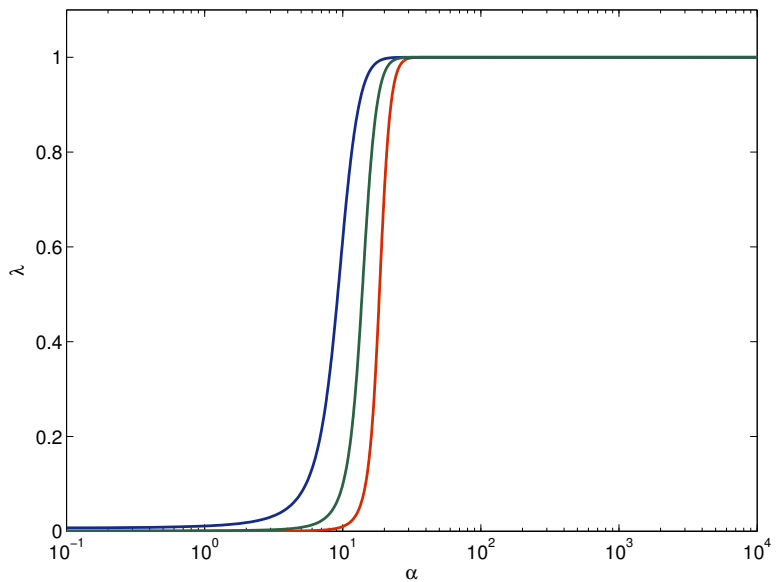
# Linear analysis predicts abrupt transition between invasive a non-invasive regimes as a function of intracellular noise

## Linear analysis

The ability of invasion by a small mutant population is provided by linearising of the dynamics of the mutant around the mutant-free steady state. In our case, this correponds to the steady state of Eqs. (3) and (4) with $n_p = n_q = 0$, i.e. $c = 1$ and $n_s = \Omega$:

$$\frac{dn_p}{d\tau} = \epsilon n_p - \epsilon w_0 e^{-\alpha/2} n_p + \epsilon w_0 e^{-\alpha/2} n_q$$

$$\frac{dn_q}{d\tau} = -\epsilon n_q + \epsilon w_0 e^{-\alpha/2} n_p - \epsilon w_0 e^{-\alpha/2} n_q$$




The blue line corresponds to $w_0 = 10^2$, the green line to $w_0 = 10^3$, and the red line to $w_0 = 10^4$

# High-noise behaviour: Emergence of latency

## Hybrid Gillespie simulation results

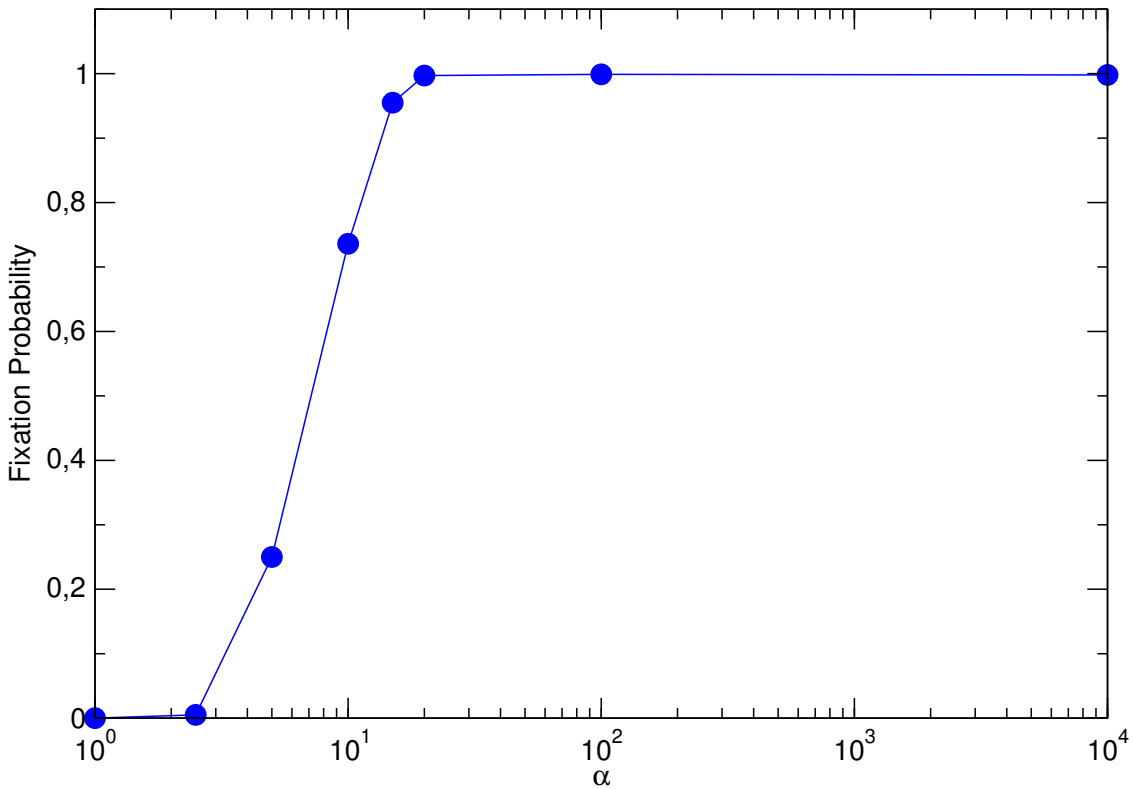
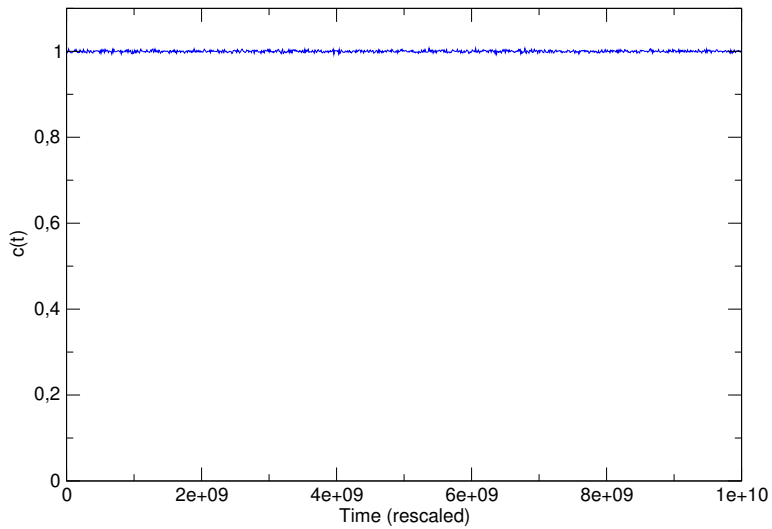
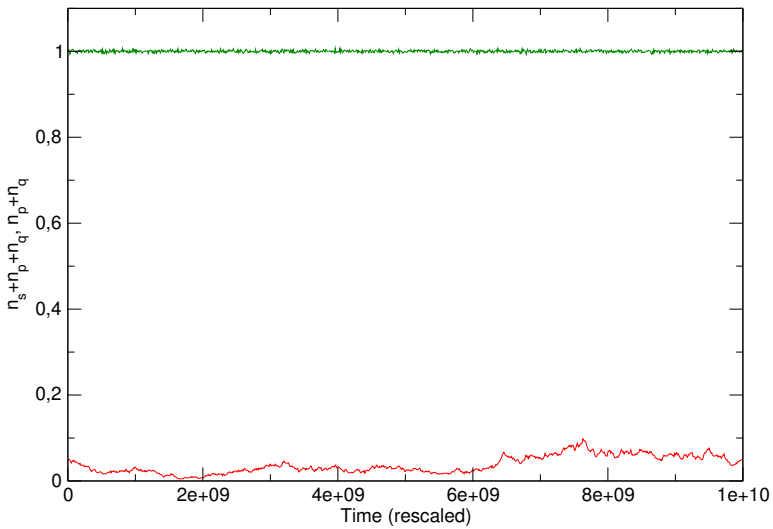



Figure : Simulation results for the fixation probability of the mutant (bistable) cell population as a function of the barrier-to-noise ratio $\alpha$. The initial mutant-to-incumbent ratio $y = 1/500$. $w_0 = 10^2$.

# The mutant population exhibits vanishing growth rate under elevated intracellular noise

## Neutral invasion dynamics




- We observe that $c(t) = c_0$
- Constant oxygen concentration implies that Switch-like cells+Proliferating cells+Quiescent cells $\simeq \Omega$
- This allows us to reduce the system and study only the dynamics of the mutant population

# Embedded branching process

In order to formulate an analytical theory, we consider the corresponding embedded branching process equivalent to our multi-type birth-death process.

## Embedded branching process

1. The process of embedding consists of a coarse-graining of time variable carryied out in the following way.
2. After birth, each individual (of type $j$) lives for a length of time which is exponentially distributed with characteristic time $\tau_c^{(j)} = \left(\epsilon(1 + w_0 e^{-\alpha/2})\right)^{-1}$.
3. At the end of their life-span, each individual produces offspring according to the corresponding generating functions of the per-cell offspring probabilities.

$$G_P(x, y) = \frac{w_0 e^{-\alpha/2}}{1 + w_0 e^{-\alpha/2}} y + \frac{1}{1 + w_0 e^{-\alpha/2}} x^2 \tag{7}$$

$$G_Q(x, y) = \frac{1}{1 + w_0 e^{-\alpha/2}} + \frac{w_0 e^{-\alpha/2}}{1 + w_0 e^{-\alpha/2}} x \tag{8}$$

4. For full specification of the age-dependent, embedded branching process, we need to give the age distribution which in this case is $f(\tau) = \tau_c^{-1} e^{-\tau/\tau_c}$.

# The embedded branching process is critical for high-noise intensity

Let M be the matrix whose entries, $m_{i,j}$, correspond to the average offspring of type $j$ produced by each individual of type $j$, simply by computing the derivatives of the generating functions: $m_{PP} = \partial_x G_P|_{x=y=1}$, $m_{PQ} = \partial_y G_P|_{x=y=1}$, $m_{QP} = \partial_x G_Q|_{x=y=1}$, and $m_{QQ} = \partial_y G_Q|_{x=y=1}$

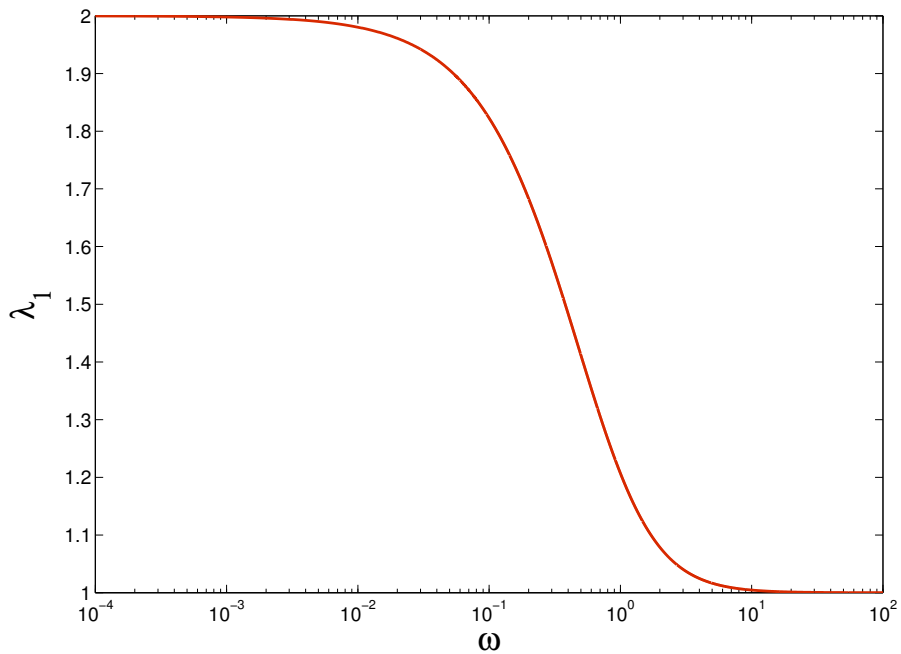
## Dominant eigenvalue of the offspring matrix

$$\mathrm{M} = \begin{pmatrix} \frac{2}{1+\omega} & \frac{\omega}{1+\omega} \\ \frac{\omega}{1+\omega} & 0 \end{pmatrix}$$

whose dominant eigenvalue is:

$$\lambda_1 = \frac{1 + \left(1+\omega^2\right)^{1/2}}{1+\omega}$$

where $\omega = w_0 e^{-\alpha/2}$



# Survival probability for critical branching processes ($\lambda_1 = 1$)

## Probability of eventual extincition ($P_E$)

1. If $\lambda_1 > 1 \Rightarrow P_E < 1$
2. If $\lambda_1 \leq 1 \Rightarrow P_E = 1$

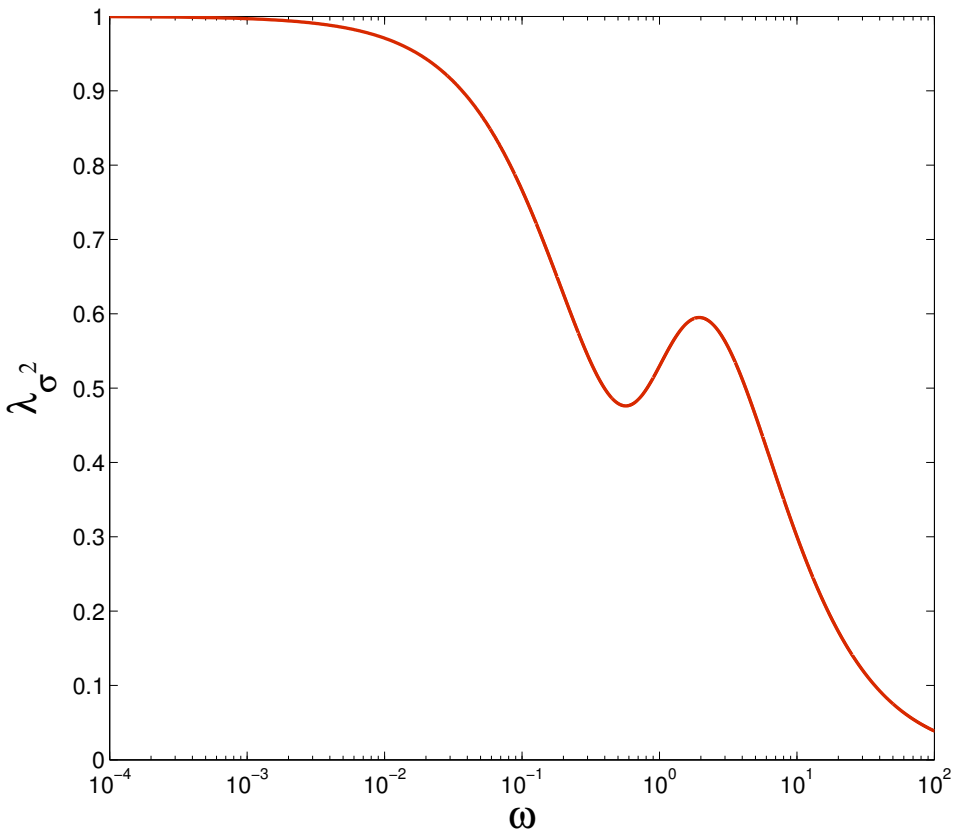
## Asymptotic behaviour of the survival probability ($P_S(t)$) for critical branching processes

- If $\lambda_1 = 1$ then $P_S(t) \sim \sigma^{-1} t^{-1}$ as $t \to \infty$
- $P_S(t) \sim t^{-1}$ implies that there is no characterstic survival time and that both short- and (aribitrarily) long-lived states are possible

# The structure of the mutant population supresses population noise ($\sigma$)

$\sigma$ is supressed as $\omega$ increases

By supressing population noise, $P_S(t)$, which is inversely proportional to $\sigma$, increases and, thus, so does the probability of latency, i.e. a state where growth is supressed by that can last for aribitraly long time



# Summary of results for well-stirred systems

Analytical and numerical results show that:

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4. The structure of the bistable population acts as a buffer for population noise, thus contributing to long-lived, growth supressed states to be more likely (latency)

# Outline

# Low-intracellular noise: Mean-field inhomogeneous model

## Mean-field inhomogeneous model

$$\frac{\partial c}{\partial \tau} = \frac{\partial^2 c}{\partial x^2} - \kappa(n_s + n_p + n_q)c, \quad \left.\frac{\partial c}{\partial x}\right|_{x=0} = h_0, \quad \left.\frac{\partial c}{\partial x}\right|_{x=L} = -h_L \tag{9}$$

$$\frac{\partial n_s}{\partial \tau} = \epsilon\nu_1 \frac{\partial^2 n_s}{\partial x^2} + \epsilon \tanh\left(\alpha_0(c-1)\right) n_s \tag{10}$$

$$\frac{\partial n_p}{\partial \tau} = \epsilon\nu_2 \frac{\partial^2 n_p}{\partial x^2} + \epsilon n_p - \epsilon w_0 P_{PA}(c) n_p + \epsilon w_0 P_{AP}(c) n_q \tag{11}$$

$$\frac{\partial n_q}{\partial \tau} = \epsilon\nu_3 \frac{\partial^2 n_q}{\partial x^2} - \epsilon n_q + \epsilon w_0 P_{PA}(c) n_p - \epsilon w_0 P_{AP}(c) n_q \tag{12}$$

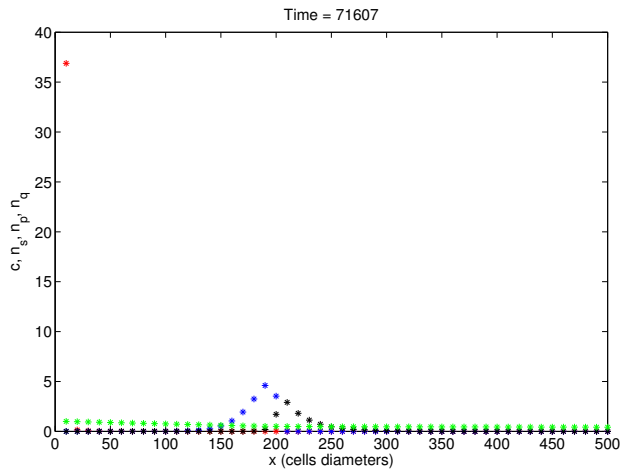
with $h_0 - h_L = Lh^{-1}\bar{\kappa}\Omega c_0$ no-flux boundary conditions for the equations for the cellular populations

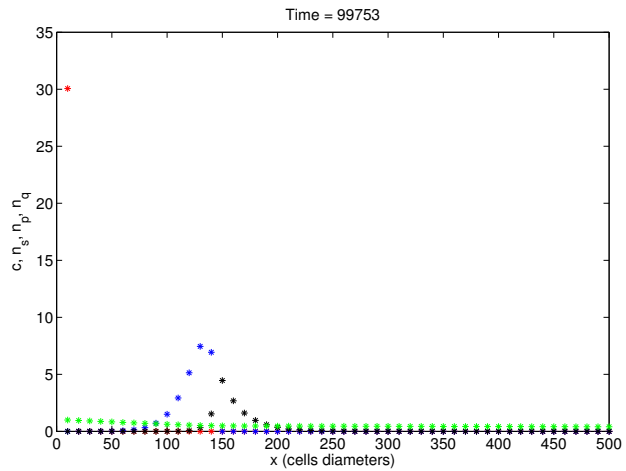
## Initial coniditions

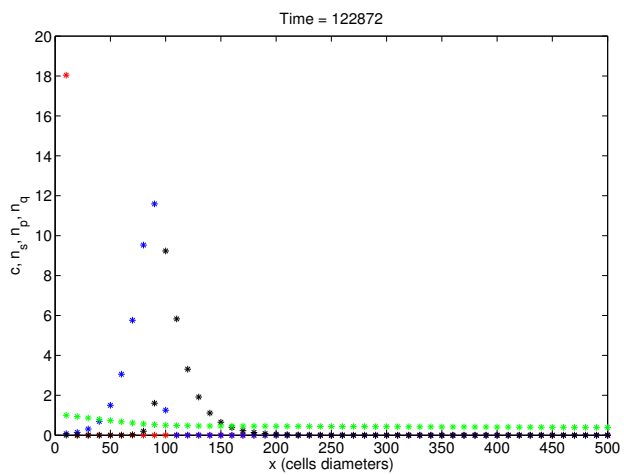
$c(x, t = 0) = 1$, $n_p(x, t = 0) = \delta(x - L/2)$, $n_q(x, t = 0) = \delta(x - L/2)$, and $n_s(x, t = 0) = \Omega/L$ if $x \neq L/2$ and $n_s(x = L/2, t = 0) = \Omega/L - 2$

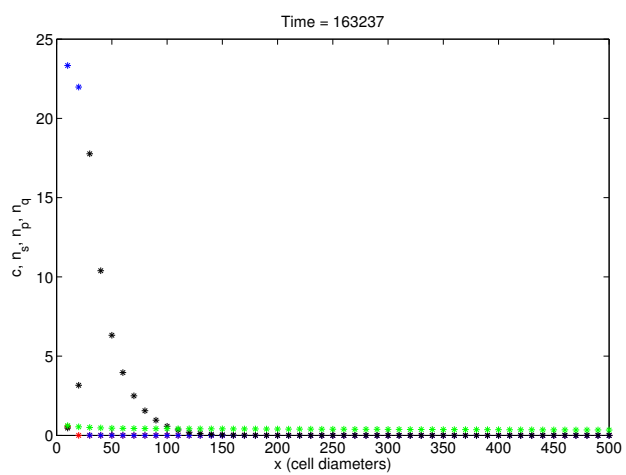
# Bistable mutant invades switch-like incumbent by migrating towards better-perfused regions

## Numerical results



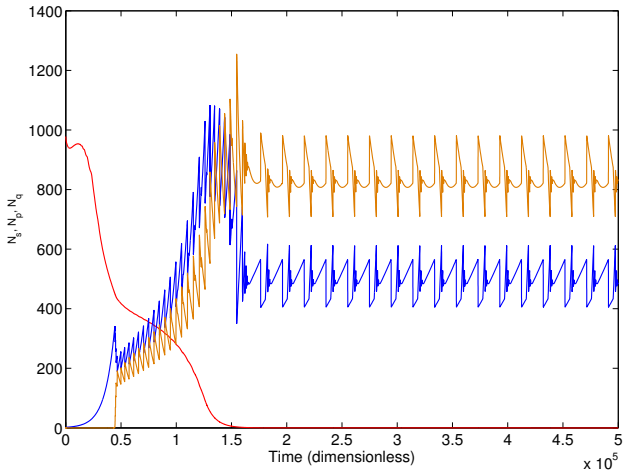



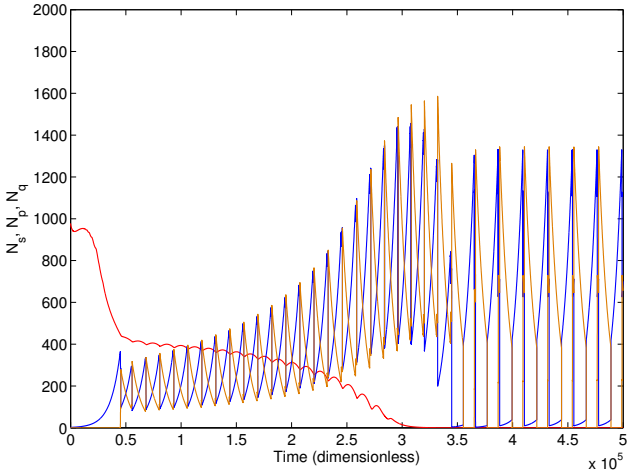
# Increased mutant motility increases its aggresiveness

## Time to incumbent extinction as a function of mutant motility

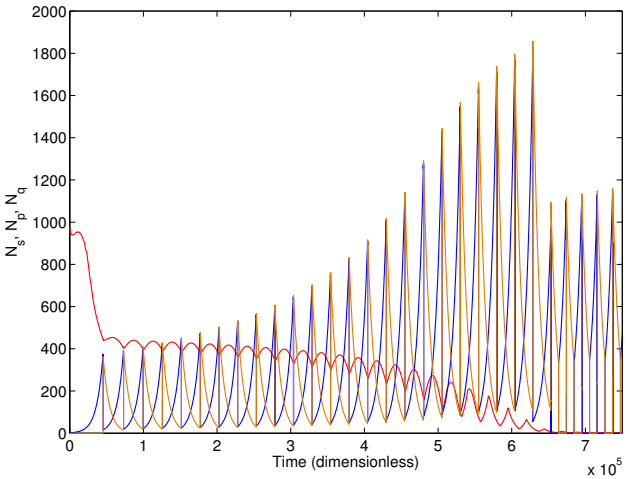
$\bar{\nu}_2 = \bar{\nu}_3 = 10^{-1}$



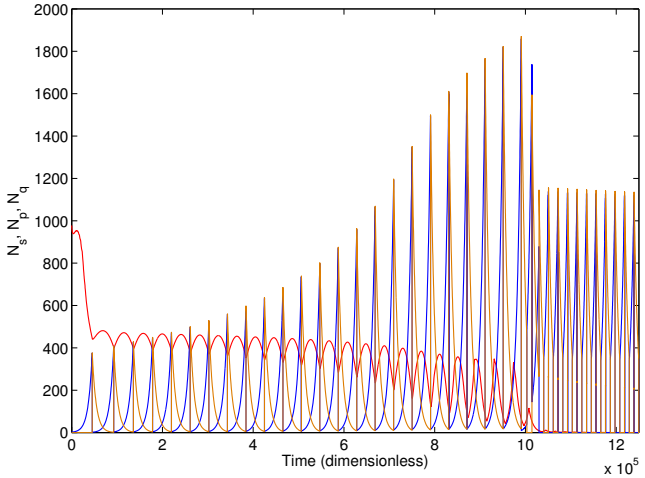

$\bar{\nu}_2 = \bar{\nu}_3 = 10^{-2}$




$\bar{\nu}_2 = \bar{\nu}_3 = 10^{-3}$

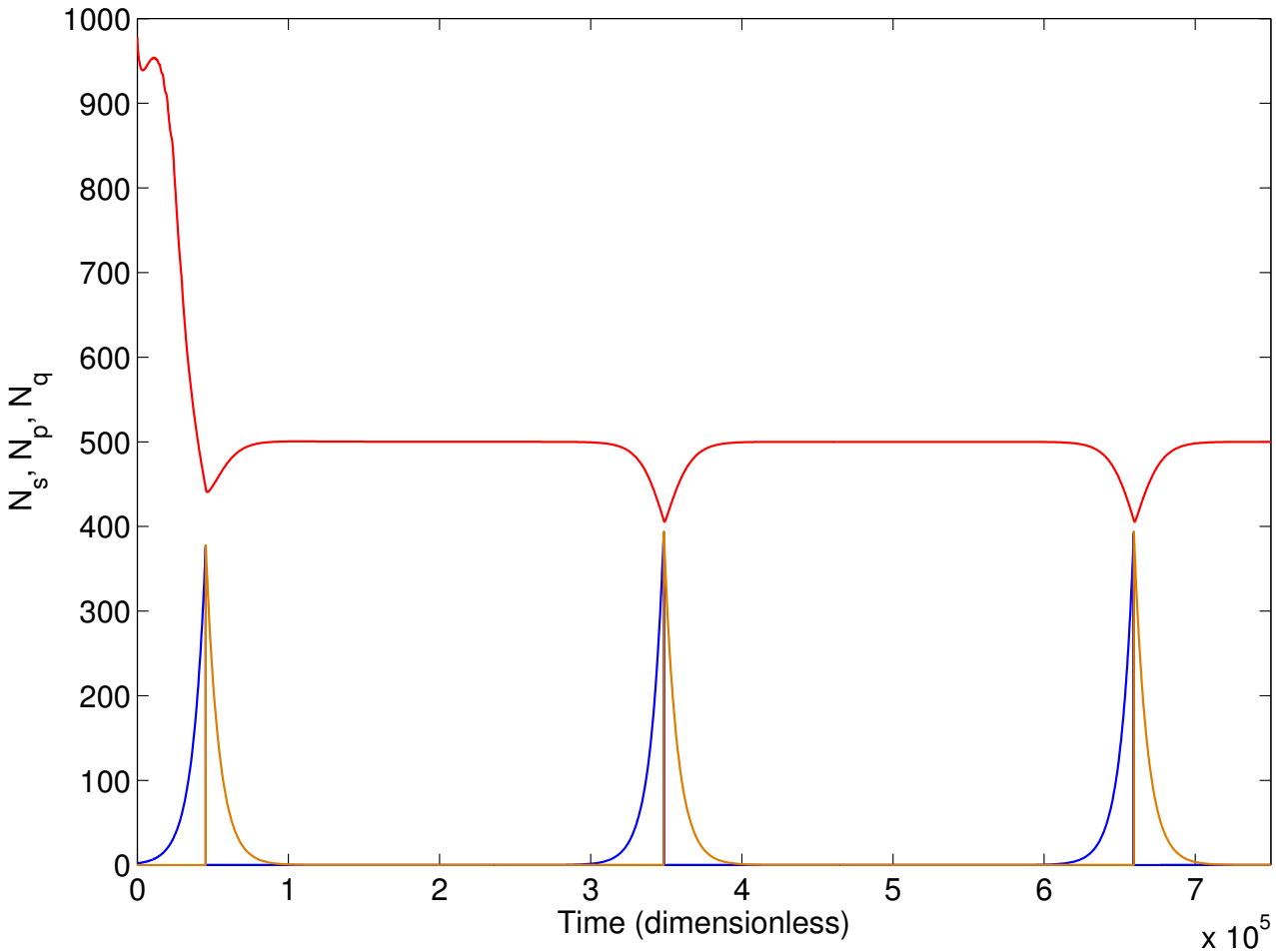



$\bar{\nu}_2 = \bar{\nu}_3 = 10^{-4}$



# Non-motile mutants are non-invasive but generate long-term coexistence

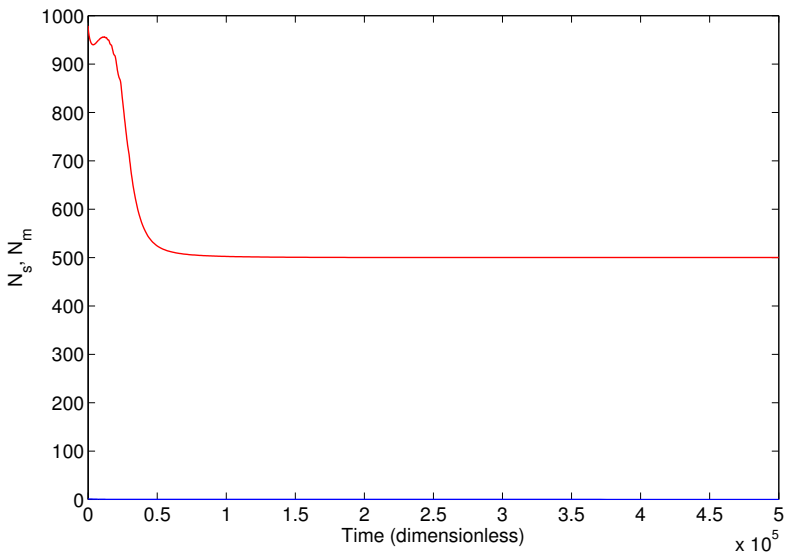
## Non-motile mutants: Stasis followed by transient bursts of mutant



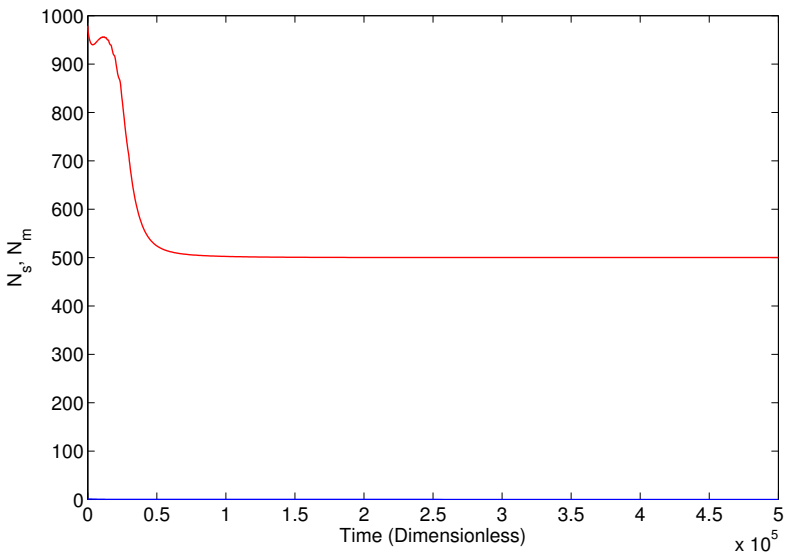
# Mere upregulation of motility is not enough for invasion

## Competition between non-motile (incumbent) and motile (mutant) switch-like populations

$\bar{\nu}_m = 10^{-1}$




$\bar{\nu}_m = 10^{-4}$



# Summary of results for inhomogeneous systems

Numerical solution of our model equations shows that:

1. Spatial inhomogeneities have a non-trivial effect on the competition between our two cell types

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Numerical solution of our model equations shows that:

1. Spatial inhomogeneities have a non-trivial effect on the competition between our two cell types
2. Increased cell motility leads to more aggresive mutants
3. Long-term coexistence between mutant and is possible provided mutant cells are not motile. This is in contrast to the well-stirred case, where no coexistence is possible for low-noise mutant cells

# Outline

# Summary & Conclusions

## Summary

- Formulation, analytical and numerical results for a model of competition between two populations characterised by two different strategies (response curves) to turn nutrients into offspring
- Intracellular noise shown to be a major factor controlling the outcome of the competition
- Increased cell motility leads to more aggresive mutants although, on its own, it is insufficient to give the advantage to the mutant (previous transformation is required)
- Coexistence between the switch-like and low-noise, non-motile bistable cells is possible in spatially homogeneous systems. It consists of long periods of stasis followed by sudden, short-lived bursts of the mutant population
- High level of intracellular noise leads to critical growth dynamics: growth-supressed states but with aribitrarily long life span

## Future work

1. Explore the therapeutic implications of our model

# Acknowledgements – Collaborators

People involved in this project

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- Helen M Byrne (Computational Biology Group & Wolfson Centre for Mathematical Biology, University of Oxford, UK)
- Philip K Maini (Wolfson Centre for Mathematical Biology, University of Oxford, UK)

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EXCELENCIA MARÍA DE MAEZTU