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MASTER THESIS

Dynamical Approach For Tumour Regression: A Cancer Stem Cell Model

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Abstract

The progression of a population of cancer cells is studied under the assumption that a small sub-population of them co-exists with cells in the usual differentiated state. This sub-population is characterised by the properties of a very peculiar state of cells: the stem state, with high proliferation rate, capacity of self-renewal and strong therapy resistance. Moreover, based on recent considerations, transitions between the two co-existing states (stem and differentiated) is allowed from stem cells to differentiated cells, but also in the reverse direction. The two transitions will however occur with different probabilities. They are governed by chemical activators and are assumed both to happen in tumours as well as in healthy tissues. Based on these considerations a model of cancer progression will be presented and simulated. It will require a sophisticated treatment of population dynamics, that will admit three fixed points. Various dynamical phenomena will be studied, and a preliminary study of the effects of a noisy environment on it will be sketched. The hope of this work is that some of the dynamical behaviours of such model will suggest good therapeutical strategies. These effects will be looked for both analytically and numerically.

Keywords *: cancer stem cells, population dynamics, extrinsic noise*

1 Introduction

1.1 About Cancer

Advances in the understanding of biological systems, in scientific knowledge and in technology have throughout the eras influenced the way of diagnosing and curing cancer. For instance the discovery in 1895 of X-ray radiations by German Physics professor Wilhelm Conrad Roentgen allowed, within a few years, the development of a new treatment for cancer called radiation therapy.

Cancer is a very devastating disease: it is the first cause of death worldwide. "The global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. One in 5 men and one in 6 women worldwide develop cancer during their lifetime, and one in 8 men and one in 11 women die from the disease" [1]. Cancer consists in the alienancy of a number of cells of the organism. Its origin is not well understood as yet, but is mostly considered to be due to genetic mutations. "Hallmarks [of cancer cells] include self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, and limitless replicative potential. Typically, this acquired characteristic leads to an abnormal increase in cells proliferation rates. Also, tumor cells can usually sustain angiogenesis and, in mid or late stages, invade other tissues and metastasize" [2]. Apoptosis is a property of cells meant to regulate their life-time, and avoid uncontrolled growth through programmed death of cells. Angiogenesis is a physiological property of cells that allows them to let veins and capillaries grow within the population itself, in order to have an easy access to nutrient and help proliferation. The self-sufficiency in growth signals is the capacity of cancer cells to regulate, through the sending of chemical signals, their capacity of renewing themselves, i.e. of generating other cells of their own kind. Once the first property is undermined and the second is active, tumour progression is ineluctable, with the activation of the third capacity. In the same way as for any healthy tissue, cancer growth depends on various environmental factors - physiological or external conditions of the body - and in the secretion of chemical substances by the cells themselves [2]. All these considerations applied to cancer make tumour progression a complex system to model: a non-monotonous behaviour, non-linearity, a high number of independent parameters and multi-dimensionality will appear to be key ingredients for its description, and make it a very striking example of complex system. It seems that a science of complexity such as the Physics of complex systems is idoneous or very welcome to address this societal and health problem. In the past few

decades, the Physics of complex systems has largely addressed ecological questions with methods of population dynamics. It was born as a science that would aim at describing collective behaviours that cannot be predicted simply on the basis of the nature of its constituents. It studies for example the evolution of an ecosystem, where species interact. The problem of cancer progression seems to have a lot to share with growth and extinction of interacting species, as various kinds of cells and chemical activators interact with one another. It therefore seems that tools coming from ecology and the science of complexity could find a very privileged place in the study of a complex mechanism such as cancer.

1.2 Approach

"The exact mechanism of spontaneous tumor remission or complete response to treatment are phenomena in oncology that are not completely understood" [3]. This clearly puts an accent on the fact that if such positive situations are not well understood and are not the most studied ones, the same uncertainty holds true for dangerous behaviours of tumours which gather most of the urgent attention of scientists. For instance, cases of tumour resumption are important to be understood. In some cases, tumour may indeed start growing dangerously after a period of quiescence. In order to explain resumption one calls forward the hypothesis that cancer cells with high proliferation rate just as if they were stem cells are present in the tumour. This is the so-called stem cell assumption. In a first moment, one will set up a deterministic model, that will be based on it, for a solid tumour that has already undergone chemotherapy. The model will allow a small sub-population of cancer cells (about 1% of the full population) to exist in the self-renewable stem state, in order to take into account cancer "self-sufficiency in growth signals" [2]. Apoptosis will play a role in the evolution of the rest of the cancer cell population, which will be found in the differentiated state. The model will only be dynamical and will not allow the tumour to spread in space, for example by flowing into veins. The tumour under study will be confined to a finite region of space, such as an organ. For this reason the model will only be addressing the behaviour of solid tumours, which are organ tumours. Organ tumours can spread, as long as they are confined to the organ. In this case, they spread in the so-called stroma or micro-environment. Within this deterministic model, one will show that the dynamics undergone by such a two-phase population of cancer cells is quite complex. The system will have to be highly non-linear and in the present case will be four-dimensional. Bringing the system to low values of the concentration of cancer stem cells will appear not necessarily to imply that the tumour will get extinct. For some values of physiological parameters, tumour may indeed start growing again. In practice, chemotherapy does sometimes have the opposite effect as the hoped and meant one: the amount of cancer stem cells might grow instead of shrinking. One will explore various cases, and will try to put forward a strategy for leading tumour to extinction, by driving it in the basin of attraction of a fixed point of the dynamical system that would correspond to an optimistic situation. "Treatment [will] not need to kill all the [cancer stem cells] to be successful in eradicating a tumor" [3].

Moreover, stochastic fluctuations of the environment surrounding the population may be important to be taken into consideration. There is experimental evidence that noise is present in cases of cancer progression [4]. The quantities that describe the physiological conditions of the region surrounding the solid tumour do fluctuate. For instance, even the simple fact that physiological temperature is different from zero, implies that there are necessary fluctuations of the system, and constant exchange with a thermal bath. Also the fact that mutations occur at different times with randomly distributed events could be a reason for the presence of noise into the system. This being said, noise may have a noteworthy impact on the system, and fluctuations due to it may be relevant for therapeutic purposes. One will therefore start exploring, in a second moment, a trivial effect

of this environmental noise on the deterministic description of the system. A striking phenomenon that could be arising, is the appearance of noise-induced jumps from one fixed point of the system to another one. Indeed, if one fixed point corresponded to tumour extinction and one corresponded to tumour survival at dangerous concentrations of cancer cells, this possibility could have positive as well as negative implications for therapy, depending on the direction of the jump. This work will bring very preliminary considerations on this stochastic part.

1.3 The Role of Stem Cells

Stem cells are characterised by high proliferation rate, capacity of self-renewal and immortality [5]. They are very present during the early stages of the development of an organism. They however do not disappear completely from the organism at the end of its development, but survive in a small percentage and play a key role in the reparation of damaged tissues. Another important characteristic of stem cells is indeed that they are toti-potent. As such, they have the power to transform into very diversely-specialised cells, through the so-called *differentiation* process. These specialised cells will be programmed to perform all the specific functions required by the particular tissue or organ they belong to. Biologists distinguish various steps within the *differentiation* process: toti-potent, pluri-potent, multi-potent and uni-potent. By sake of simplicity, one will not consider intermediate steps. Once differentiated, cells loose toti-potence and become uni-potent, or differentiated. Stem cells undergo what will be referred to as "mitosis", in reference to the proliferation process that cells normally undergo, but in a broader sense. It will indeed gather in it two of the properties of stem cells which were mentioned above: capacity of self-renewal and *differentiation* -the former describing the normal occurrence of mitosis. After such a generalised "mitosis", daughter cells will be either stem or differentiated ones. In the former case, the mother stem cell has renewed itself, in the latter case it has undergone *differentiation*.

Observations show that cells exhibiting a cancerous behaviour are cells that belong to a given tissue and that are thus generally specialised. But these observations do not necessarily imply that stem cells cannot be present in tumours. Indeed, a reason for the lack of observations thereof could be that stem cells are not only usually present in a low percentage but also very difficult to detect [5]. Anyways, the idea that cancer cells may be found in the stem state is still the matter of heavy debate. The assumption that tumours do contain cancer stem cells could however explain the development, by some of them, of therapy resistance as well as uncontrolled growth in quasi-homeostatic cancers. Indeed, in quasi-homeostatic cancers, differentiated cells do not have particularly strong growth rates. Therefore, in these conditions, the uncontrolled growth of the tumour could well be explained by the presence in the population of special cells with high proliferation rate. Their presence could also explain several biological facts such as the relapse of tumour post-surgery or the ability to generate tumours in xeno-transplantations, depending on the injected mass [5]. Leukemia, pancreatic cancer, squamous cell carcinoma, colon cancer and melanoma are examples of tumours which seem to contain sub-populations of cancer cells in the stem state [6]. However, leukemias will not be the matter of this work, since they are blood tumours and hence not solid.

In this work, the approach to the problem of cancer progression will be made within the assumption that some small percentage of the full population will be composed of cancer cells in the highly proliferating stem state.

A recent perspective also considers that, in healthy cells, the transition from stem state to differentiated state is not the only one to occur. Cells may also undergo the opposite transition ; differentiated cells thus recovering their toti-potence, with some rate. There is strong experimental evidence that such a reverse process occurs [7]. It is called *de-differentiation*, as opposed to *differentiation*. This perspective was envisaged after Gurdon's and Yamanaka's works leading to a

technique bringing differentiated cells back to their stem state. The resulting cells are called *induced stem cells* (iSC). By transplanting mouse differentiated cells (fibroblasts) into a mouse embryo, they discovered that all the genetic material necessary for recovering the toti-potence of stem cells does not get lost along the *differentiation* process. In particular, Yamanaka discovered that four genes are alone responsible for toti-potence of cells, meaning that this capacity of stem cells is carried by a support, genes, that does not get lost during *differentiation*. In fact, fibroblasts would start contributing to the formation of various tissues inside the hosting embryo.

De-differentiation in healthy cells, is a strategy of survival for the population. Stem cells are able to self-renew as well as to differentiate. They are thus capable of letting a population grow or of keeping it in a homeostatic state, in which population's size is pretty much constant in time. This being said, there may arise situations that would let the number of stem cells significantly decrease and may even threaten their survival. In order to avoid this, the differentiated cells are capable of undergoing a *de-differentiation* process, which will let the sub-population of stem cells recover its initial size, against dramatic damages done on the tissue. As an example of what happens in healthy populations of cells, in cases of strong diarrhea, a large portion of the intestinal cells may be lost through it, thus threatening the integrity and the reconstruction of the intestinal wall. Thankfully, in this case, some of the differentiated cells left are allowed to switch back to the stem state, in order to recover a minimum size for the sub-population of stem cells. Once this minimal size has been reached, the population of healthy stem cells will possibly be able to efficiently reconstruct the damaged tissue.

Recent works have also shown that this backward process not only occurs in healthy cells, but may also occur in cancer ones too [4]. Although *de-differentiation* is much less common compared to the *differentiation* process, it may play a key role in the creation of a feedback which could for example explain the occurrence of tumour resumption.

Because of the inclusion of the *de-differentiation* process, the present model lies in between two already-existing models: the hierarchical and the stochastic one. The former does not consider *de-differentiation*, so that eventually, complete extinction of the cancer stem cells will eradicate the tumour. It however takes self-renewal of cancer stem cells into account. On the other hand, the latter, the so-called stochastic model, considers that any kind (stem or differentiated) of cells can possibly be a tumour-initiating one. It thus does consider *de-differentiation* but not self-renewal.

As for the initial conditions of the population under study, if concentrations are initially already important, the uncontrolled growth of the tumour seems unavoidable. In order to have a chance of escaping the case of uncontrolled growth, the model will therefore have to consider cases in which initial concentrations are relatively low. This way, one will be able to describe tumour extinction as well as tumour resumption and other behaviours. Such an initial condition on the concentrations of cancer cells can for instance occur after a treatment by chemotherapy, or at an early stage of tumour growth.

In short, the model which will be presented hereafter will be based on the cancer stem cell assumption according to which tumours contain a sub-population of stem cells. In particular three of the characteristics of stem cells will be relevant: their capacity of self-renewal, *differentiation* and *de-differentiation*. In the case of low initial concentrations, these aspects aim at explaining various behaviours of tumours.

2 Deterministic Model

As mentioned above, the model consists in letting cells of the system be found into two different states: the stem and the differentiated ones. It is a dynamical model of the ecological kind, in the continuous limit for the variables S, D, a and m. Variables in fact are discrete quantities as they describe population concentrations. They evolve in time in a way that depends on various regulation quantities. The growth and decay of the cancer cell concentrations is for instance governed by chemical activators responsible for either self-renewal of cancer stem cells or *de-differentiation* undergone by differentiated cancer cells. The model overall follows the time-evolutions of the four variables (S, D, a and m), in a coupled way and according to the following set of nonlinear differential equations [5]:

$$\begin{cases} \frac{dS}{dt} = \Big(\frac{2\eta a}{(1+\eta a)(1+\psi D)} - 1\Big)S + \frac{q_0}{2}(1 + tanh(\frac{m-m_0}{\sigma}))D, & (1) \\ \frac{dD}{dt} = 2\Big(1 - \frac{\eta a}{(1+\eta a)(1+\psi D)}\Big)S - (d + \frac{q_0}{2}(1 + tanh(\frac{m-m_0}{\sigma}))D, & (2) \\ \frac{da}{dt} = a(\beta S\frac{a}{1+a} - \alpha), & (3) \\ \frac{dm}{dt} = \gamma e^{-\frac{S}{S_0}} - \alpha m. & (4) \end{cases}$$

S is the concentration of cancer ***s***tem cells, D is that of cancer ***d***ifferentiated cells. "In practice, in vivo and in vitro, the population of cancer stem cells is always a tiny fraction of the entire tumour population (few percents)"[5]. Both quantities being concentrations, their sum must always stay below unity: $S + D < 1$. The remainder to unity will constitute a third phase of the model, which has not been mentioned yet. This third phase contains quiescent, dead and immune T cells [5] that are present in tumours although in a passive way. It in fact does not appear explicitly in the present model. The variables a and m are the concentrations of both chemical activators governing self-renewal and *de-differentiation* respectively. One will now proceed to the listing of the main physical properties included in this model.

- The activator a is responsible for the self-renewal of cancer stem cells. It indeed appears in the growth term of S in eq. 1. It is produced by cancer stem cells themselves. This justifies the linear dependence of the growth term of a on S (eq.3). This growth however saturates with a saturation coefficient $\frac{a}{1+a}$. "Candidate self-renewal promoters include Wnts, BMP, Shh, and Notch" [8].

- The activator m, on the other hand, is responsible for the *de-differentiation* process, i.e. for the re-population of S. Since S undergoes a proliferation process that one decided to hereafter call "mitosis", through which differentiated cells D can be born, the re-population of S ultimately implies that of D [5]. Above a value $m = m_0$, m strongly contributes to the growth of the concentration of cancer stem cells, through a sigmoid function $q(m) = \frac{q_0}{2}(1 + tanh(\frac{m-m_0}{\sigma}))$. This function describes the *de-differentiation* rate as a function of the activator m and carries its main action on the system. The sigmoid appears in the positive contribution to the growth of cancer stem cells S (eq. 1), and to the negative term in the growth of differentiated cells D (eq.2). The value of $\frac{S}{S_0}$ regulates the growth of m. The quantity m may represent the concentration of the protein *survivin* which has been shown to promote *de-differentiation* in cell lung cancer of mice [3], but also "a network of miniRNA" [5]. The latter "promote[s] the awakening of quiescent breast cancer stem cells from a mesenchymal to an epithelial state" [9].

- q_0 is the maximum rate at which *de-differentiation* happens, when it does occur (i.e. if $\sigma << 1$, this happens approximately when $m > m_0$). In fact, when $m > m_0$, $q(m) \to q_0$, whereas in the opposite case, $q(m) \to 0$.

- S_0 is a critical value for the growth of m. For values of S that are very large compared to S_0, the growth term $(\gamma e^{-\frac{S}{S_0}})$ in the evolution of m will go to zero, so that only the death term will drive its evolution (eq. 4). In cases of very large $S >> S_0$ there will therefore be an effective decay of the concentration of m. In other words, when many stem cells are present, the chemical activator responsible for the *de-differentiation* process is not called forward. On the other hand, for concentrations of cancer stem cells very small compared to S_0, the positive contribution will tend to its maximum value γ, in order to re-populate S. In short, for very low concentrations of cancer stem cells ($S << S_0$), the *de-differentiation* activator m will have a non-vanishing growth term, and may even effectively grow. The overall variation of m is very sharp around $S \sim S_0$. The $\gamma e^{-\frac{S}{S_0}}$ term finally carries what has been described above as the survival strategy of the population.

- d carries the effective death rate of differentiated cells: it contains both proliferation and death of D. It in fact appears as a coefficient in the negative contribution to their growth (eq.2). Examples of processes of cellular death are apoptosis, senescence and autophagy. "The case where $d < 0$, due to proliferation of differentiated cells via nutrients is not considered, since it leads to an exponential growth in the population of both stem and differentiated cells" [5]. For this reason, the present model describes a quasi-homeostatic tumour. Cancer stem cells are not assumed to undergo similar spontaneous death process: they are immortal. Hence, the absence of death rate in the equation for the evolution of S (eq.1).

- α represents the death rate of both chemical activators (see equations 3 and 4). It is by sake of simplicity that they were chosen to take the same value.

- $d, q_0, \alpha, \beta, \eta, \psi, m_0, \sigma, \gamma, S_0 > 0$. All parameters are positively defined. They are related to physiological quantities which can be measured in experiments.

For what concerns the coefficients of S in the first two equations of the system, one should consider in greater detail the cell division process. A cancer stem cell divides into two daughter cells through mitosis. As anticipated, in this model one will consider a very schematic and generalised division process which will include processes that are not present in simple mitosis, such as *differentiation*. One will hereafter call it "mitosis", into quotes. Based on the state in which the daughter cells are found, one may distinguish three different cases. There are two cases of symmetric "mitosis". In the one case, the two daughter cells are both born in the stem state. In the other case, they are both born in the differentiated one. The asymmetric situation, on the other hand only counts one case: one daughter cell is in the stem state and the other one is in the differentiated state.

Let p be the probability that a cell division originates one stem cell. The contribution to the growth of S, as a result of the division of S itself, also called self-renewal coefficient, will therefore simply be $(2p-1)$. Indeed, one is trying to determine how "mitosis" lets the number (concentration) of cancer stem cells grow in time. It replaces one mother cancer stem cell by two daughter cells. If the daughter cells are both stem, "mitosis" will enable a net increase of the number of cancer stem cells: from one to two. The probability that two stem cells are born through "mitosis" will trivially be twice the probability p that one stem cell is. However, since the mother stem cell disappears in the process, one must subtract it, as it will no longer be able to contribute to the growth of the S population. The stem cell self-renewal coefficient is finally $(2p - 1)$ [3].

When it comes to the growth of D, as a consequence of the mitosis of S one will show that the contribution is simply $2(1-p)$. Indeed, it can happen either when one differentiated cell is born through "mitosis" (asymmetric case), or when two differentiated cells are (symmetric case). In the former case, the net growth of D will be by one unity, and will happen with probability $(1-p)$. The latter, will be associated to a net growth by two unities, thus with probability $2(1-p)$. Overall, the *differentiation* will contribute to the growth of D with the following coefficient: $(1-p)+\frac{1}{2}\times 2(1-p) = 2(1-p)$. Since mitosis, in the narrow sense of self-renewal, in our model is only undergone by cancer stem cells, there is no disappearance term for D. One can also check that the total probability is well normalised to 1: $2p-1+2-2p=1$.

The shape of p can be taken as follows [8]:

$$p = p(D,a) = \frac{\eta a}{(1+\eta a)(1+\psi D)} \tag{5}$$

As mentioned above, the quantity a is responsible for the self-renewal of S. For this reason p must be proportional to a. As the population cannot grow indefinitely a saturation term is included. Saturation will be regulated by both the amount of activator a and the concentration of differentiated cells D. The larger the amount of differentiated cancer cells, the less the need of the cancer stem cells population to let itself get bigger. One has thus shown that the coefficients of s are indeed $(\frac{2\eta a}{(1+\eta a)(1+\psi D)} - 1)$ and $2(1 - \frac{\eta a}{(1+\eta a)(1+\psi D)})$ in equations 1 and 2, respectively.

The proliferation of differentiated cells does not appear in the model. In fact one considers that, in the absence of external action, the differentiated cells are found in a quasi-homeostatic state. All the energy they consume would be sufficient and just enough for keeping themselves in a stable situation, in which individuals do not die nor divide with a particularly high rate. Homeostasis is the "tendency to [stay in] a relatively stable equilibrium between interdependent elements, specially as maintained by physiological processes. The regulation of [...] homeostasis involves the competition for a limited supply of diffusible factors" [10].

Chemotherapy targets cancer stem cells S, as these drugs are meant to attack rapidly dividing cells [3]. In a model where differentiated cells are taken in a quasi-homeostatic state, they cannot be the target of chemotherapy. The effects of chemotherapy will moreover only be taken into consideration as possibbly responsible for the low initial values of the concentrations of cancer cells, required by the model. Indeed, the goal of this work is to study the free evolution of cancer from such an initial condition.

To summarize, the model has incorporated dynamical statements which were previously made in a qualitative way, on cancer. Among these statements, one has shown that the dynamics contains the *differentiation* of cancer stem cells, its self-renewal and the activation of the *de-differentiation* process above a small threshold value S_0 for the concentration S of cancer stem cells. Whereas stem cells do not die, differentiated cells undergo apoptosis. An activator (a) is involved in the regulation of cancer stem cell self-renewal. Another activator (m) will govern *de-differentiation*. Both evolve as functions of the concentrations of cancer stem cells. One is interested in understanding the behaviour of such a system depending on the values of the parameters, which can be determined experimentally. The study of its dynamics therefore starts with the determination of the fixed points of the system. Fixed points are meaningful because they correspond to conditions for which the system stops evolving in time. They are stationary and homogeneous solutions of the system.

2.1 Fixed Points

Four quantities have been pointed as involved in the process of tumour growth. The system of equations describing their coupled time-evolutions has been presented. The vector describing the evolution of the system lives in a four-dimensional space, whose axes are (S, D, a, m). In the same way as for any dynamical system, the fixed points of this particular one can easily be determined. Fixed points are defined by the coordinates that let the system's motion (carried by the time derivative) vanish. Since we deal with a four-dimensional system, each fixed point will be defined through four coordinates. By imposing $\frac{da}{dt} = 0$ in the set of equations of paragraph 2, one agrees that there are two solutions for a:

$$a(\beta S \frac{a}{1+a} - \alpha) = 0 \quad \Rightarrow \quad a = 0 \quad \text{and} \quad a \doteq a_3,$$

where a_3 is the solution for $\beta S \frac{a}{1+a} - \alpha = 0$. In order to determine the coordinates of the fixed points one will proceed in two steps. One will first determine all the fixed points satisfying to the condition $a = 0$ and then determine the ones that satisfy to the complementary one $a = a_3$. One will finally have covered all possible cases. The expression $S = dD$ is true whichever the value of a (see Appendix .1).

- In the case where the activator responsible for self-renewal of cancer stem cells is totally absent, i.e. $a = 0$, putting the left-hand-sides in the system of equations in paragraph 2 equal to zero leads to the following two fixed points (see Appendix .2):

$$\mathcal{F}_1 = \begin{cases} S_1 = 0, \\ D_1 = 0, \\ a_1 = 0, \\ m_1 = \frac{\gamma}{\alpha}, \end{cases} \qquad \mathcal{F}_2 = \begin{cases} S_2 = -S_0 log(\frac{\alpha m_2}{\gamma}), \\ D_2 = \Big[- S_0 log(\frac{\alpha m_2}{\gamma}) \Big] \frac{1}{d}, \\ a_2 = 0, \\ m_2, \end{cases}$$

  with $m_2 = \sigma tanh^{-1}(2\frac{d}{q_0} - 1) + m_0$, obtained by plugging $S = dD$ in eq. 2 of the system of equations and by recalling that $a = 0$.

  Whereas $\mathcal{F}_1$ is always defined, $\mathcal{F}_2$ is only defined for $d < q_0$ and $m_2 < \frac{\gamma}{\alpha}$. One can prove these statements analytically by observing the expression for m_2. Because of the domain of the inverse hyperbolic tangent, m_2 is in fact only defined for $2\frac{d}{q_0} - 1 < 1$, so indeed for $d < q_0$. As for the second condition of existence, one needs to impose that the concentrations of cells S_2 and D_2 will only admit positive values - otherwise leading to unphysical results. As a consequence, the argument of the logarithm in the expressions for the concentrations will have to be always larger than one:

$$\frac{\alpha m_2}{\gamma} > 1 \quad \Rightarrow \quad m_2 > \frac{\gamma}{\alpha} \tag{6}$$

- As for the case where $a = a_3$, there is only one corresponding fixed point (Appendix .3):

$$\mathcal{F}_3 = \begin{cases} S_3 = \frac{\alpha}{\beta} \frac{1+a_3}{a_3}, \\ D_3 = \frac{1}{d}(\frac{\alpha}{\beta} \frac{1+a_3}{a_3}), \\ a_3 = \frac{1}{2} \frac{1 + \frac{\Psi_\alpha}{d\beta}(1+\eta)}{\eta(1 - \frac{\Psi_\alpha}{d\beta})} \Big(1 + \sqrt{1 + \frac{4 \frac{\Psi_\alpha}{d\beta} \eta (1 - \frac{\Psi_\alpha}{d\beta}))}{(1 + \frac{\Psi_\alpha}{d\beta}(1+\eta))^2}} \Big), \\ m_3 = \frac{\gamma}{\alpha} exp(-\frac{S_3}{S_0}). \end{cases}$$

Similarly to the second fixed point $\mathcal{F}_2$, $\mathcal{F}_3$ does not exist for all values of d and q_0. It is only defined for $d > \frac{\psi\alpha}{\beta}$. Indeed, the value of a_3 would be negative if $\frac{\Psi\alpha}{d\beta}$ were larger than 1 and a negative concentration of chemical activator would be unphysical. The requirement of having $a_3 > 0$ therefore yields the following condition on the death rate d, for the existence of $\mathcal{F}_3$:

$$\frac{\Psi\alpha}{d\beta} < 1 \quad \Rightarrow \quad d > \frac{\Psi\alpha}{\beta}. \tag{7}$$

The line $d = \frac{\Psi\alpha}{\beta}$ is the horizontal one appearing in the (d, q_0)-phase-diagramme in Fig.1. For Fig. 1's specific choice of parameters, its value is $\frac{\Psi\alpha}{\beta} = 5$.

As for the physical interpretation of these points, the first fixed point $\mathcal{F}_1$ corresponds to the most optimistic situation in which concentrations of cancer cells in both states -S and D- are strictly equal to zero. The second one, $\mathcal{F}_2$, too, is associated to an optimistic situation. Indeed, once the values of the parameters chosen, the concentrations S and D are not exactly vanishing, yet, they are generally quite low. On the other hand, the third fixed point $\mathcal{F}_3$ is a very pessimistic one. Even though tumour converging to $\mathcal{F}_3$ stabilises to a steady state and does not further proliferate, the steady state is associated to high concentrations of cancer cells, which makes the situation dangerous.

One has obtained the coordinates of the points of parameter space for which the dynamics of the system vanishes. The model will then be based on the study of their stability for the construction of what could be a good therapeutic strategy: one will study the basins of attraction of each of the three fixed points, in order to find the regions of the (d, q_0)-parameter-space to which it would be sufficient to lead the system, in order for it to converge to either of the optimistic fixed points, $\mathcal{F}_1$ or $\mathcal{F}_2$. One will see that this region is the blue region in the phase-diagramme of Fig. 1.

2.2 Stability Analysis

Once the fixed points determined, one is interested in studying the stability of the system around them. The stability analysis is done locally by linearizing the system around each of the fixed points and calculating the eigenvalues. One can extract the eigenvalues of the system around each fixed point by:

- Treating one fixed point at a time.
- Evaluating the Jacobian at the chosen fixed point.
- Calculating the corresponding characteristic polynomial.
- Finding its roots. Roots are the eigenvalues of the chosen fixed point.

The Jacobian has matrix coefficients given by:

$$\begin{pmatrix} \frac{\partial eq1}{\partial S} & \frac{\partial eq2}{\partial S} & \frac{\partial eq3}{\partial S} & \frac{\partial eq4}{\partial S} \\ \frac{\partial eq1}{\partial D} & \frac{\partial eq2}{\partial D} & \frac{\partial eq3}{\partial D} & \frac{\partial eq4}{\partial D} \\ \frac{\partial eq1}{\partial a} & \frac{\partial eq2}{\partial a} & \frac{\partial eq3}{\partial a} & \frac{\partial eq4}{\partial a} \\ \frac{\partial eq1}{\partial m} & \frac{\partial eq2}{\partial m} & \frac{\partial eq3}{\partial m} & \frac{\partial eq4}{\partial m}, \end{pmatrix}$$

where $eq1, eq2, eq3$ and $eq4$ are the right-hand-sides of the differential equations in the system of paragraph 2. It becomes:

$$\begin{pmatrix} 2p(D,a)-1 & 2S\frac{\partial p(D,a)}{\partial D}+q(m) & 2S\frac{\partial p(D,a)}{\partial a} & \frac{\partial q(m)}{\partial m}\cdot D \\ 2(1-p(D,a)) & -2S\frac{\partial p(D,a)}{\partial D}-(d+q(m)) & -2S\frac{\partial p(D,a)}{\partial a} & -\frac{\partial q(m)}{\partial m}\cdot D \\ \frac{\beta a^2}{1+a} & 0 & \frac{\beta S a(a+2)}{(a+1)^2}-\alpha & 0 \\ -\frac{\gamma}{S_0}exp(\frac{-S}{S_0}) & 0 & 0 & -\alpha. \end{pmatrix} \tag{8}$$

where:

$$p(D,a)=\frac{\eta a}{(1+\eta a)(1+\psi D)} \quad \text{and} \quad q(m)=\frac{q_0}{2}(1+tanh(\frac{m-m_0}{\sigma}))$$

$$\frac{\partial p(D,a)}{\partial D}=\frac{-\eta\psi a}{(1+\eta a)(1+\Psi D)^2} \quad \text{and} \quad \frac{\partial p(D,a)}{\partial a}=\frac{\eta}{(1+\eta a)^2(1+\psi D)}$$

$$\frac{\partial q}{\partial m}=\frac{q_0}{\sigma}(1+tanh(\frac{m-m_0}{\sigma}))\Big[1-\frac{1}{2}(1+tanh(\frac{m-m_0}{\sigma})\Big].$$

With the eigenvalues in hand, the stability of the fixed points will then be controlled by the signs of the eigenvalues and the amplitude of their imaginary part. If all eigenvalues are positive, the fixed point will be repulsive. If all eigenvalues are negative, it will be attractive. In mixed cases, it will be saddle. Each eigenvalue is associated to an eigenvector. The eigenvector, carries the direction along which the system shows the stability described by the corresponding eigenvalue. It is straight if the imaginary part is zero and spiraling otherwise.

One will analyse the stability numerically. Analytical stability analysis can be found in appendices.

2.3 Stability of $\mathcal{F}_1$

One recalls that the first fixed point takes coordinates $\mathcal{F}_1 = (0, 0, 0, \frac{\gamma}{\alpha})$. One may check that $S_1 + D_1 = 0 \leq 1$. What remains in the body when tumour cells disappear are cells of the third phase mentioned in section 2 : quiescent, dead and immune.

• In a case for which $d > q_0$ (red region of the phase diagramme in fig. 1) :

$$\text{For: } \begin{cases} d = 2 \\ q_0 = 1 \\ \alpha = 1 \\ \beta = 3 \end{cases} \quad \Rightarrow \quad \text{Eigenvalues are: } \begin{cases} \lambda_{1,2} = -1 \\ \lambda_3 = -3.7 \\ \lambda_4 = -0.27 \end{cases} \tag{9}$$

All four eigenvalues are negative. Hence, $\mathcal{F}_1$ is stable.

• In a case for which $d < q_0$ (green region) :

$$\text{For: } \begin{cases} d = 0.2 \\ q_0 = 1 \\ \alpha = 0.5 \\ \beta = 5 \end{cases} \quad \Rightarrow \quad \text{Eigenvalues are: } \begin{cases} \lambda_{1,2} = -0.5 \\ \lambda_3 = -2.52 \\ \lambda_4 = 0.32 \end{cases} \tag{10}$$

For this second choice of parameters, the first fixed point is saddle. λ_4 is in fact positive.

One can show analytically (Appendix .4) that more generally, the first fixed point is stable as long as $d > q_0$, and saddle otherwise. Biologically, the condition $d > q(m)$ means that the death rate of the differentiated cancer cells is shorter than the time-scale for *de-differentiation*. Differentiated cells die much more quickly than the time necessary to let them transform back to stem cells. As a consequence, it does not seem surprising that both cancer stem and differentiated cells vanish in the first fixed point.

In both cases, the values of the missing parameters were the following: $\eta = 1, \psi = 0, m_0 = 0.5$, $\sigma = 0.05$, $\gamma = 1$, $S_0 = 0.038$.

2.4 Stability of $\mathcal{F}_2$

The second fixed point is only defined for $d < q_0$ (green region).

$$\text{For: } \begin{cases} d = 0.2 \\ q_0 = 1 \\ \alpha = 0.5 \\ \beta = 5 \end{cases} \quad \Rightarrow \quad \text{Eigenvalues are: } \begin{cases} \lambda_{1,2} = -0.81 \pm 3.24i \\ \lambda_3 = -0.5 + 0i \\ \lambda_4 = -0.19 + 0i \end{cases} \tag{11}$$

For this choice of parameters, the second fixed point takes coordinates $\mathcal{F}_2 = (0.05, 0.27, 0, 0.46)$. ($S_2 + D_2 = 0.05 + 0.27 = 0.32 \leq 1$ is respected.) The values of the missing parameters were the following: $\eta = 1, \psi = 1, m_0 = 0.54$, $\sigma = 0.05$, $\gamma = 1$, $S_0 = 0.038$. When it exists, $\mathcal{F}_2$ is attractive, with two spiraling directions for each of the two eigenvectors corresponding to $\lambda_{1,2}$. Indeed all four real parts are negative, and two of the imaginary parts are non-vanishing. An analytical proof of the attractiveness of $\mathcal{F}_2$ can be found in Appendix .5.

2.5 Stability of $\mathcal{F}_3$

The stability of the third fixed point $\mathcal{F}_3$ is particularly relevant as it is the one fixed point that therapies urge to avoid.

• In a case where $d > q_0$ (red region) :

$$\text{For: } \begin{cases} d = 2 \\ q_0 = 1 \\ \alpha = 1 \\ \beta = 3 \end{cases} \quad \Rightarrow \quad \text{Eigenvalues are: } \begin{cases} \lambda_{1,2} = -1.01 \pm 0.28i \\ \lambda_3 = -1 + 0i \\ \lambda_4 = 0.81 + 0i \end{cases} \tag{12}$$

For this choice of parameters, the third fixed point takes coordinates $\mathcal{F}_3 = (0.53, 0.26, 1.72, 9.3 \times 10^{-7})$. $S_3 + D_3 = 0.79 \leq 1$

• In a case where $d < q_0$ (green region) :

$$\text{For: } \begin{cases} d = 0.2 \\ q_0 = 1 \\ \alpha = 0.5 \\ \beta = 5 \end{cases} \quad \Rightarrow \quad \text{Eigenvalues are: } \begin{cases} \lambda_{1,2} = -0.23 \pm 0.18i \\ \lambda_3 = -0.5 + 0i \\ \lambda_4 = 0.47 + 0i \end{cases} \tag{13}$$

For this second choice of parameters, the third fixed point takes coordinates $\mathcal{F}_3 = (0.15, 0.73, 2.15, 0.042)$. $S_3 + D_3 = 0.88 \leq 1$ in this case too.

In both cases, the values of the missing parameters are the following: $\eta = 1, \psi = 1, m_0 = 0.5$, $\sigma = 0.05$, $\gamma = 1$, $S_0 = 0.038$.

For both $d < q_0$ and $d > q_0$ cases, two eigenvalues have a non-vanishing imaginary part, meaning that the dynamics around the third fixed point will be spiraling along two directions. However, since the real parts of these eigenvalues are negative, both the corresponding directions will be attractive. The same will hold true for the direction associated to the fourth eigenvalue, i.e. the one which had a negative real part and no imaginary part at all. There will overall be three attractive directions for the system around the third fixed point $\mathcal{F}_3$, and a repulsive one. The repulsive one will be given by the eigenfunction associated to the last eigenvalue λ_4, which has a positive real part and a vanishing imaginary part.

To sum up, around the third fixed point, one direction is repulsive, one is attractive and two are attractive along spirals.

The third fixed point will therefore be a saddle point. This is proven analytically in Appendix .6. One may check this in the phase diagramme (Fig. 1) and in the streamline plots (Fig. 4 and Fig. 5) as well. The point of coordinates $(S, a) = (0.15, 2.15)$ in the left-hand-sided picture of Fig. 4 has both attractive and repulsive streamlines crossing it.

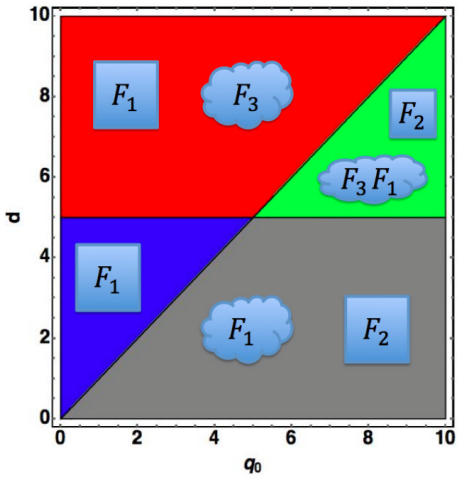

Figure 1: [5]. Phase-diagramme for existence and stability of fixed points in the plane of parameters d and q_0 ([5]). Fixed points into boxes are stable. Fixed points into clouds are saddle. The equation for the horizontal line is $d = \frac{\psi\alpha}{\beta} = 5$. The equation for the bisectrix is $d = q_0$.

2.6 Global Dynamics

After having studied the local dynamics around the three fixed points of the system, one is ready to get results from a less local point of view. One will first summarise all results mentioned in the previous section within a phase-diagramme. One will then proceed to the study of some particular cases of time-evolution of the variables of the system. One will finally look at the specific shape and size of the basins of attraction around the fixed points. As an opening to future work, one will expose some very preliminary considerations concerning noise-induced changes in stability.

2.6.1 Phase-Diagramme

In order to summarise what has been determined above concerning the existence and stabilities of the three fixed points, one will plot the various regions delimited by the conditions of existence. However, the amount of free parameters in the model is much too important to allow a full representation. One will therefore have to discriminate relevant from irrelevant parameters. Among the 10 parameters $(d, q_0, \alpha, \beta, \eta, \psi, m_0, \sigma, \gamma, S_0)$, one may show that only 6 are relevant in the dynamics of the population of cancer cells: d, q_0, α, β, η and ψ.

One is in fact interested in those parameters which are relevant for the definition of regions of parameter-space where the dynamics is not completely divergent. In fact, in diverging situations, only relatively trivial therapeutic strategies can be extracted. For the same reason, our model describes a population of cancer cells after chemotherapy, i.e. when tumour growth has already been significantly controlled. For initial high concentrations of cancer cells, the dynamics will hardly escape uncontrolled growth.

For instance, in the (d, q_0)-two-dimensional sub-space shown in Fig. 1, two-to-three fixed points are defined, and different sub-regions show different stability configurations. This particular sub-space is strikingly relevant as conditions of existence for the fixed points could both be plotted. Stability considerations made in the previous section are well summarised in this figure. One can see that $\mathcal{F}_2$ is not defined above the bisector $d = q_0$, and when it exists it is stable. In the region

where this relatively optimistic fixed point does not exist, however, the very optimistic fixed point $\mathcal{F}_1$ exists and is stable. The pessimistic third fixed point $\mathcal{F}_3$ is saddle whenever it exists ($d < \frac{\psi\alpha}{\beta}$).

One easily observes that the blue region is a very optimistic one as the fixed point $\mathcal{F}_1$ associated to vanishing concentrations of cancer cells is stable and is even the only one existing in it. An idea would then be to base a therapeutic strategy on this result, by imposing that the system be in that situation. A strategy that would first come to mind, and that reminds of the goal of chemotherapy itself, is that of targeting cancer cells, by inducing their death. This would correspond in the model to increasing the value of the death rate d of differentiated cells. However, the simple condition of maximisation of d appears not to completely escape the possibility that tumour converges to a steady-state with high concentration of cancer cells. Indeed, in the phase-diagramme of Fig. 1, the red and the green regions have higher values of death rate d, but are regions in which the pessimistic fixed point $\mathcal{F}_3$ exists and threatens the system.

If one wants to drive the system to the blue region, then, one needs to impose the following two inequalities: $q(m) < d < \frac{\psi\alpha}{\beta}$ (which define this region).

- One possibility is to have $m < m_0$. This makes the hyperbolic tangent in $q(m) = \frac{q_0}{2}(1 + tanh(\frac{m-m_0}{\sigma}))$ go to -1 thus canceling the *de-differentiation* rate $q(m) \to 0$. The first inequality defining the blue region will then automatically be satisfied, since, in the present model, d is always positive. The second inequality on the other hand will suggest a strategy. If one increases the value of α as much as to make the fraction $\frac{\psi\alpha}{\beta}$ larger than the death rate d, the second inequality will have good chances to be satisfied, thus imposing that the system be in the optimistic blue region of the phase-diagramme. In other words, in the case where $m < m_0$, a strategy that seems promising for therapy is that of increasing the spontaneous death rate α of both the activators a and m.

- In the case however where $m > m_0$, the value of the hyperbolic tangent will be close to 1. This will let the *de-differentiation* rate $q(m)$ be approximately equal to q_0. Since $q(m) \leq q_0$, by definition, if $d > q_0$, the same situation as above holds: the first inequality will be satisfied and a promising strategy would be the action on the death rate α of the activators, in order to let the second inequality hold true as well. On the other hand, if $d < q_0$, the first inequality will never be satisfied. But for $d < q_0$, one knows that the second fixed point $\mathcal{F}_2$ is attractive. An alternative procedure would then be to lower the values at which the system will want to stabillise to, i.e. to lower the values of S_2 and $D_2 = \frac{S_2}{d}$. This leads us back to a maximisation of α strategy. One in fact recalls that:

$$S_2 = -S_0 log\Big(\frac{\alpha}{\gamma}(\sigma tanh^{-1}(\frac{2d}{q_0} - 1) + m_0)\Big).$$

  Since S_0 is positive, the argument of the logarithm will have to be the larger in order for S_2 to take low values. Then:

$$\frac{\alpha}{\gamma}(\sigma tanh^{-1}(\frac{2d}{q_0} - 1) + m_0) \to 1,$$

  which will be the more likely to be satisfied, the larger the value of α.

2.6.2 Dynamical Simulations

The goal of this work being to study the dynamical behaviour of a multi-phase population of cancer cells, one will be particularly interested in following the time-evolutions of the four variables of

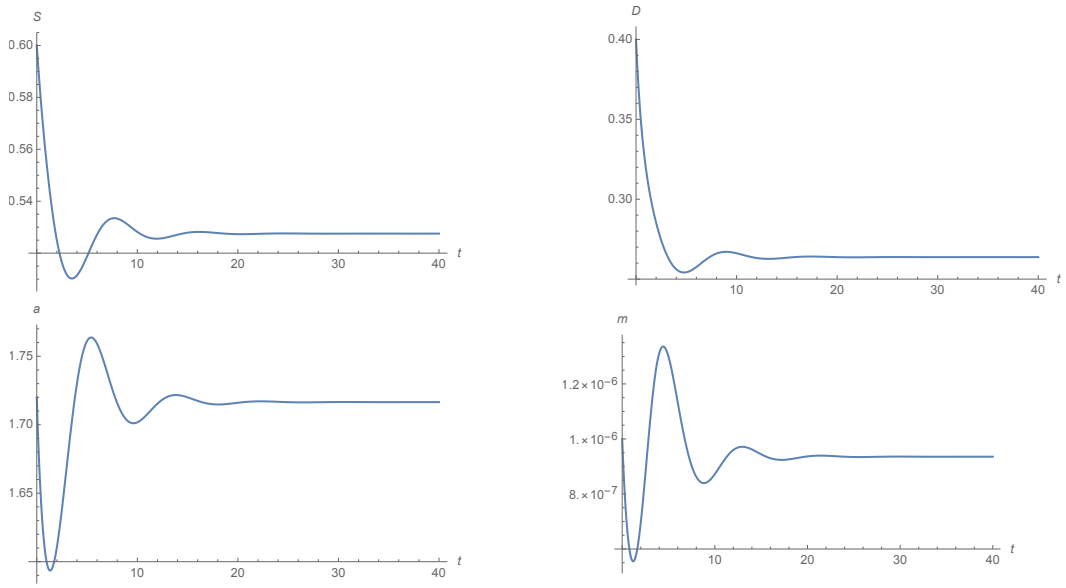

Figure 2: Evolution in time of S, D, a and m. Initial conditions are $S(0) = 0.6$, $D(0) = 0.4$, $a(0]) = 1.72$, $m(0) = 0.000001$. Values of parameters are $(d, q_0) = (2, 1)$, $(\alpha, \beta, \eta, \psi, m_0, \sigma, \gamma, S_0) = (1, 3, 1, 1, 0.5, 0.05, 1, 0.038)$, corresponding to a system in the red region of the phase-diagramme.

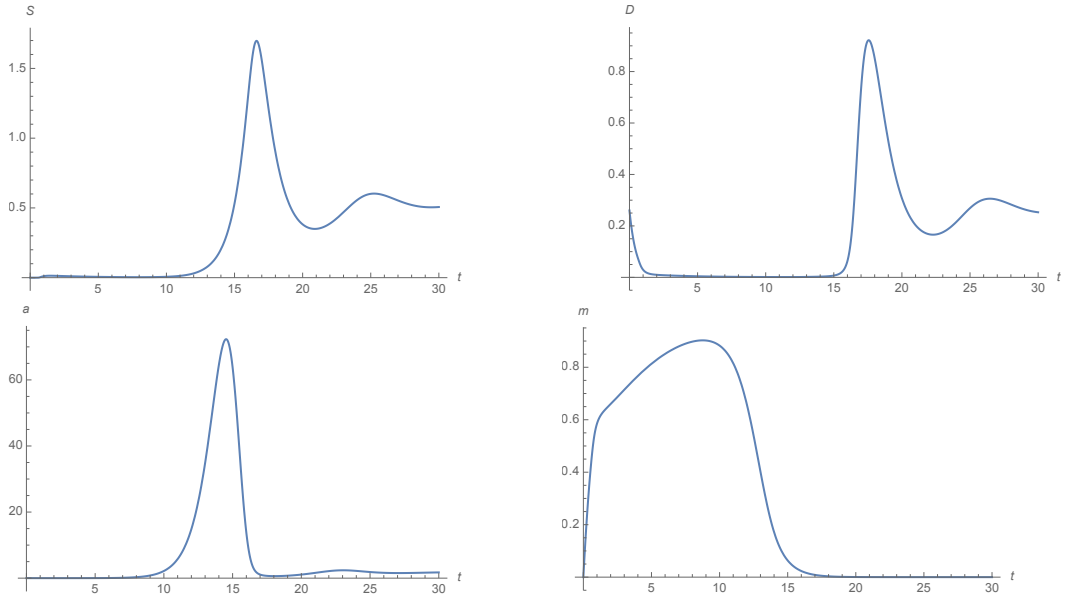

Figure 3: Dynamics of the system with the following set of initial conditions: $S(0) = S_1 = 0, D(0) = D_3 = 0.26, a(0) \sim a_1 = 0.0001, m(0) = m_3 = 9.3 \times 10^{-7}$. Parameters are: $(d, q_0) = (2, 1)$, and $(\alpha, \beta, \eta, \psi, m_0, \sigma, \gamma, S_0) = (1, 3, 1, 1, 0.5, 0.05, 1, 0.038)$. The system is in the red region of the phase-diagramme, and jumps from the first fixed point $\mathcal{F}_1$ at zero concentration of cancer cells, to the third fixed point $\mathcal{F}_3$, standing at high concentrations.

the model, given different initial conditions. In order to plot these evolutions one has solved the differential equations using the Euler method with Python and using NDSolve with Mathematica.

Fig. 2 shows that the variables S, D, a and m oscillate in time around a fixed point before converging to it. This oscillating dynamics is the translation of the fact that some eigen-directions were found to be spiraling in the stability analysis.

For some sets of initial conditions, one can see that jumps from one fixed point to another may arise, in a completely deterministic situation. This is simply due to a proximity of the initial conditions to two different fixed points, which will let the system first converge to one of them and, after some time, converge to the other one. The time after which the system will change its mind, will depend on the initial conditions. Fig. 3 shows that for the chosen initial conditions I, the system jumps from the first fixed point $\mathcal{F}_1$ to the third one $\mathcal{F}_3$, after approximately 15 iterations of time. Compared coordinates of I, $\mathcal{F}_1$ and $\mathcal{F}_3$ are the following:

$$I = \begin{cases} S_i = 0, \\ D_i = 0.26, \\ a_i = 0.0001, \\ m_i = 9.3 \times 10^{-7}, \end{cases} \qquad \mathcal{F}_1 = \begin{cases} S_2 = 0, \\ D_2 = 0, \\ a_2 = 0, \\ m_2 = 1, \end{cases} \qquad \mathcal{F}_3 = \begin{cases} S_3 = 0.53, \\ D_3 = 0.26, \\ a_3 = 1.72, \\ m_3 = 9.3 \times 10^{-7}, \end{cases}$$

For the choice of parameters that lead to Fig.3 ($(d, q_0) = (2, 1)$, $(\alpha, \psi, \beta) = (1, 1, 3)$), the system stands in the red region of the phase-diagramme (Fig.1). The death rate $d = 2$ is larger than the *de-differentiation* rate $q_0 = 1$. This choice corresponds to an attractive fixed point $\mathcal{F}_1$. However, one could think that for this value of d one stands in the blue region, since $d < 5$. This is not the case, because the horizontal line will be shifted to a value $d \neq 5$. In fact, for the new choice of parameters, $d = \frac{\alpha\psi}{\beta} = 0.33$ which is lower than the chosen value $d = 2 > 0.33$. The system does stand in the red region.

Despite the fact that in that region, the attractive fixed point is $\mathcal{F}_1$, the concentration of cancer stem cells S, in the upper left plot of Fig. 3, jumps drastically from $S_1 = 0$ to $S_3 = 0.53$ around the 15-th iteration of time, thus over-crossing the stable fixed point $\mathcal{F}_1$.

2.6.3 Tumour Resumption

The overall stability of the system around the fixed points has been shown as a function of d and q_0 in the phase-diagramme (Fig. 1). The evolution has been confirmed from a purely dynamical point of view in time-plots. For some initial conditions of the variables the system has shown a more complex behaviour, including jumps from one fixed point to another. The goal is now to have a closer look at the exact shape and speed of the streamlines around the fixed points, in the variable-space. A streamline plot shows trajectories and directions of the system in a two-dimensional sub-space. The rainbow gives a measure of the norm of the vector field. Figures 4 and 5 show streamline plots in both (S, a)- and (D, a)-subspaces for two different choices of parameters. One has used Mathematica and has fixed the two variables of the system that do not appear in the plot at the values they take in the third fixed point $\mathcal{F}_3$. What is being followed is therefore the convergence of the system to any of the fixed points, given that two of its variables are already in $\mathcal{F}_3$. This brings uones back to the complex behaviour mentioned here above, that involved jumps in the dynamics. Indeed, in the previous case, the values of D_i and m_i were exactly equal to D_3 and m_3 respectively, just like for the (S, a)-plots in Figures 4 and 5. One may notice the important changes in size of the basins of attraction from one choice of parameters (red region) to the other one (green region).

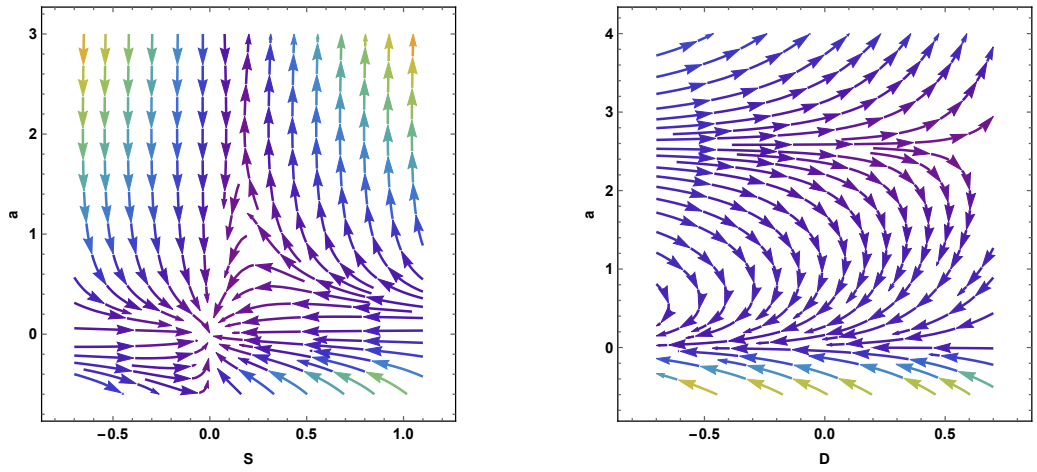

Figure 4: Streamplot for $d < q_0$ (green region): $(d, q_0) = (0.2, 1)$; and $(\alpha, \beta, \eta, \psi, m_0, \sigma, \gamma, S_0) = (0.5, 5, 1, 1, 0.5, 0.05, 1, 0.038)$.

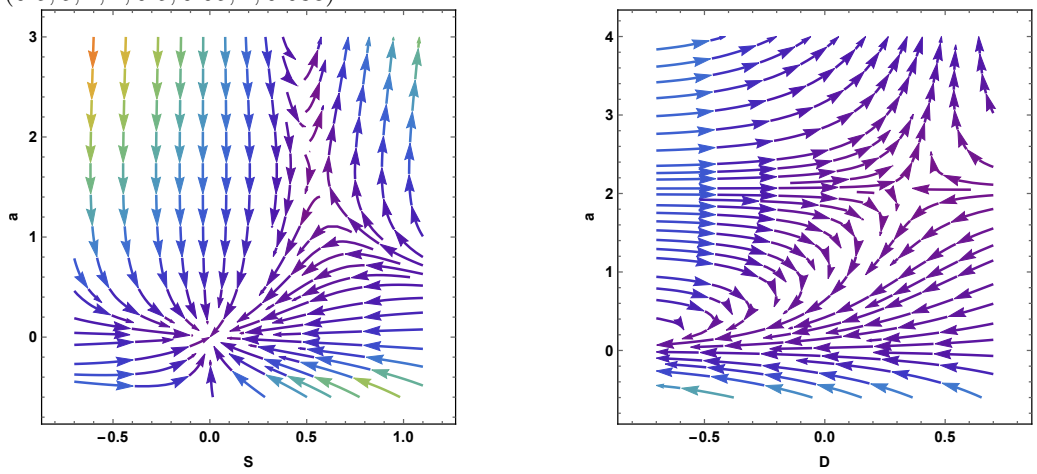

Figure 5: Streamplot for $d > q_0$ (red region): $(d, q_0) = (2, 1)$, and $(\alpha, \beta, \eta, \psi, m_0, \sigma, \gamma, S_0) = (1, 3, 1, 1, 0.5, 0.05, 1, 0.038)$.

In the streamline plots, one can see that the system may undergo regression, resumption, and convergence to a fixed point, depending on their position in (S, a)- and (D, a)-subspaces. In Figures 4 and 5, the basins of attraction of the two figures on the right-hand-side (in the (D, a)-subspace) are more or less comparable. However, their difference in size in the left-hand-sided pictures (in the (S, a)-subspace) are quite different. In the red region (Fig. 5), the size of the basin of attraction for low concentration values is larger compared to the green region's case (Fig. 4), where, moreover, the optimistic fixed point $\mathcal{F}_1$ is no longer stable. Driving the system to the basin of attraction of $\mathcal{F}_{1,2}$ is therefore more restrictive in the green region: it is a more dangerous region for the system to be in.

In other words, in the red regions, where $\mathcal{F}_1$ is stable, the Allee effect [3] is more likely to occur with extinction of cancer cells. The Allee effect is a cooperation phenomenon defined as the positive correlation between population density and average fitness. Allee had proved in an ecological setting that aggregation can improve the survival rate of individuals, as well as the opposite statement. The Allee effect is indeed also defined at low population densities as a tendency of it to shrink. The extinction of tumour could be explained as some sort of cooperative behaviour of cancer cells "that become[s] less efficient at low population density" [11]. It may arise as a consequence of "autocrine growth factors, diffusive signalling molecules produced and secreted by cells that enhance growth and proliferation of other cells" [11]. So finally, "due to feedback and the Allee effect, a tumor may become extinct spontaneously or after therapy even when the entire tumor has not been eradicated by the end of [it]" [3].

In the less dangerous red region, it appears that, even though the attractive fixed point is $\mathcal{F}_1$, the tumour will not necessarily go under regression and converge to such low concentrations of cancer cells, because of the existence of the third fixed point $\mathcal{F}_3$. In order to impose that the system will eventually converge to $\mathcal{F}_1$, one would think qualitatively, that inducing death of differentiated cells by acting on their death rate d, would be a good strategy. Indeed, the case of the red region, with larger d, at fixed q_0, seemed more optimistic than that of the green region with lower d. However, this does not seem to be a very promising strategy, since the red region still threatens of making the system's concentrations of cancer cells grow dangerously.

In continuity with what was mentioned in paragraph 2.6.1, one is interested in checking that acting on parameter α could instead have more positive consequences on the system. In the streamplots of Fig. 6, one observes that the higher the value of α, the wider the basin of attraction for optimistic fixed points $\mathcal{F}_1$ and $\mathcal{F}_2$.

2.6.4 Noise-Induced Change in Stability

Environmental fluctuations can certainly influence the dynamics of the system. Indeed, their presence in the system can lead it out of the initial basin of attraction, thus changing its asymptotic behaviour. This can for instance be because the quantities describing the system fluctuate, or because the basins of attraction do so. Figure 7 shows the fluctuations of the basins of attraction as induced by an additive gaussian white noise for d and q_0 of standard deviations 0.9 and 0.6 respectively. Noise has been defined as a function of time. However, since streamline plots are independent of time, noise has simply been obtained by evaluating the function at some fixed time. At each iteration of the noise the full function is redefined. This is the way that was chosen among others for extracting a random number from a gaussian distribution, with Mathematica. One may observe that the basin of attraction of $\mathcal{F}_1$ sometimes shrinks significantly. As a consequence of these large changes in size of the basins of attraction, noise-induced transitions from one fixed point to another seem likely to occur. However, it is not surprising that with such an important noise variance, the system will jump from one fixed point to the other. Moreover, this does not allow to define any therapeutic strategy, as transitions induced in such a way would be purely random.

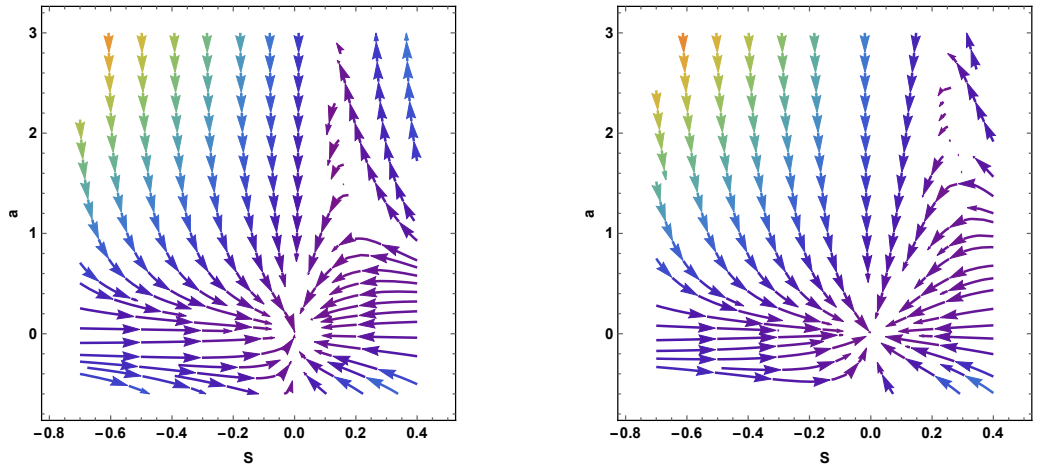

Figure 6: Parameters common to both figures are: $(d, q_0) = (0.2, 1)$, $(\beta, \eta, \psi, m_0, \sigma, \gamma, S_0) = (5, 1, 1, 0.5, 0.05, 1, 0.038)$; (green region). The figure on the left-hand-side has lower value of the death rate of the activator responsible for self-renewal of cancer stem cells: $\alpha = 0.5$. Figure on the right-hand-side has stronger death rate: $\alpha = 0.9$.

One would therefore want to look for noteworthy effects of relatively weak noise on the system, that would not occur in a random way. For the definition of a good therapeutic strategy, one would like to see whether noise could make the system be very likely to converge to either of the optimistic fixed points.

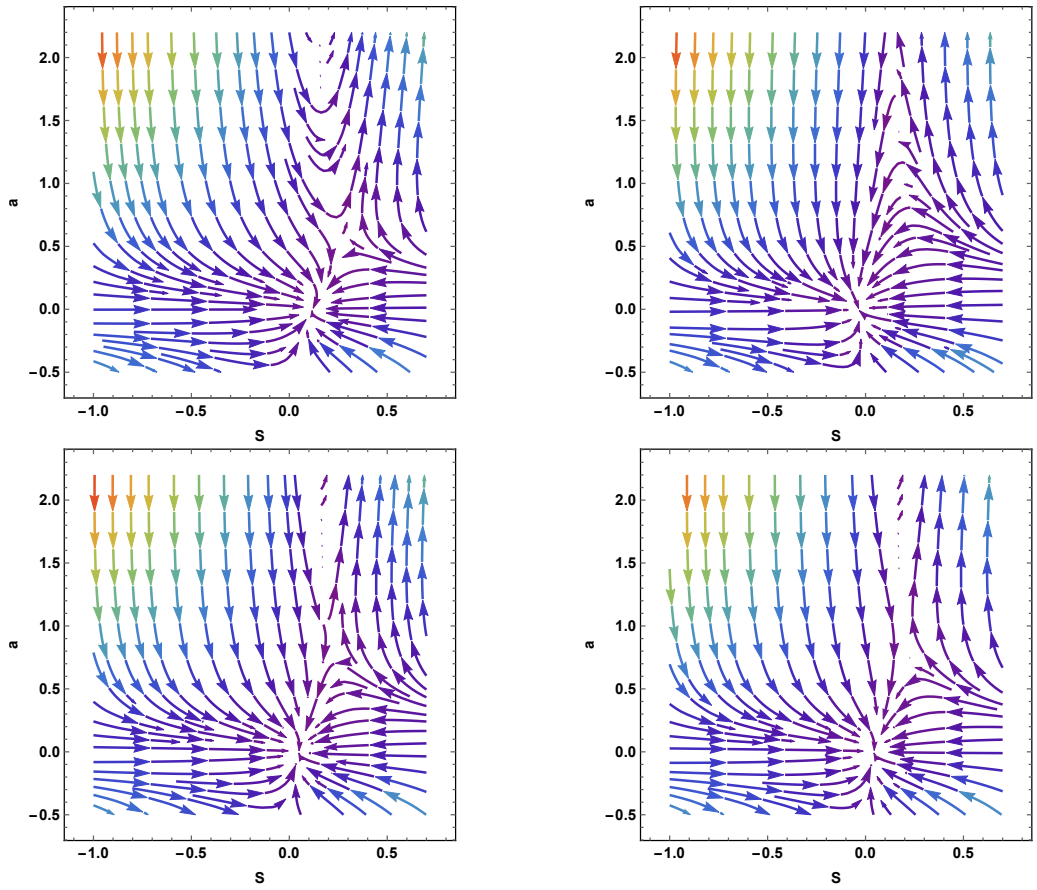

Figure 7: Streamplots for four different realizations of noise. Parameters are: $(d, q_0) = (0.2, 1)$, $(\alpha, \beta, \eta, \psi, m_0, \sigma, \gamma, S_0) = (0.5, 5, 1, 1, 0.5, 0.05, 1, 0.038)$; - Green region.

3 Conclusion

A simple multi-phase model for tumour progression has been presented, and simulated. In particular, one is dealt with a bi-phase model: the cancer population was assumed to be composed of a small percentage (about 1%) of cancer cells in the stem state of cells, the rest of the population was instead present in the differentiated state. The model for cancer then took into consideration transitions among the two allowed states of cells. This model is meant to describe non-trivial phenomena such as tumour resumption that seem to take place in some kinds of cancer. Tumour resumption occurs if a population with low concentrations of cancer cells - a situation which would seem optimistic - starts resuming, or growing dangerously again. A few examples of cancers that sometimes exhibit such a behaviour are pancreatic cancer, squamous cell carcinoma, colon cancer, melanoma and breast cancer [4].

The transition from stem to differentiated cells is the one that occurs most frequently within a population and is called *differentiation*. It consists in cells in their toti-potent stem state to differentiate into a given tissue's or organ's specialised cells and thus to switch to the so-called differentiated state. The opposite transition, from differentiated to stem state, happens, on the other hand, much more seldom. Its existence in tumours, however, may be the one responsible for events of tumour resumption, which are not yet well understood. This transition that takes the name of *de-differentiation*, occurs when the amount of cells in the stem state goes below some small threshold value which was denoted S_0. The differentiated cells will then act in order to repristinate an "acceptable" concentration of stem cells. The possibility of backward transition that occurs in healthy cells thus introduces in the cancerous situation the feedback that could explain the occurrence of tumour resumption.

One has numerically and analytically observed that, depending on the region of variable-space, the cancer system may undergo regression, resumption or convergence to a steady-state that was more or less optimistic.

The first therapeutic strategy that came to mind was that of inducing senescence or a stronger death rate on the differentiated cells by increasing the value of d. However it is not necessarily a good strategy as the situation of large death rate, $d > q_0$, has been shown not to be so optimistic. Indeed, the presence of the third fixed point in the red and green parts of the phase-diagramme made it not automatically true that a regression would take place.

The ideal case has been shown to be the one corresponding to the blue region of the phase diagramme, for lower values of d. The idea was then to base a good therapeutic strategy on this result, by imposing the system to be in that situation. This was shown to find optimistic response when imposing a growth of the spontaneous death rate α of the activators. The most promising strategy therefore seemed to be that of targeting chemical activators rather than cancer cells themselves, because of the vicious feedback loop occurring between stem and differentiated cancer cells [5]. "In medical centers nowadays, this strategy is commonly employed post-surgery to avoid the relapse of a new tumour at the same place of the primary one which had been withdrawn. Long time drug administration over years aims at suppressing these activators" [5].

The study of the conditions under which jumps occur also seemed relevant for the determination of promising therapeutic strategies. One has shown that for some choices of initial conditions, the system jumps from one fixed point to another one. The hope is to further explore both deterministic and noisy situations that induce such changes of asymptotic behaviour, so that therapy could avoid jumps leading to a pessimistic steady-state, and promote those leading to an optimistic one.

Since research in stochastic processes has shown that noise may have a strong impact on non-linear systems, and since noise is necessarily present in this system, it seems important to check for possible effects of noise on it. The work on this stage has been interrupted at a very preliminary

point. But various ideas are in process.

Analysis and simulations of this model allowed to determine parameters for which resumption happens, as well as parameters for which a change of basin of attraction occurs, after an amount of time that depends on the initial conditions. The model has hopefully enabled to draw a provisional conclusion on possible therapeutic strategies for tumour extinction [5]. The hope of the success of such a model is that it may also allow a more personal medical monitoring. Based on parameter values that are related to physiological quantities, one could decide the strategy to adopt, in order that, given the basin of attraction in which the patient is initially found, the cancerous system will eventually be brought to extinction.

4 Appendices

.1 Proof: $S = dD$

One should take the first pair of equations in system of equations of paragraph 2. Since one is ultimately looking for the coordinates of the three fixed points, one lets the time-derivatives vanish.

In order to simplify notations one recalls that:

$$\frac{\eta a}{(1+\eta a)(1+\psi D)} = p$$

The system finally simplifies into:

$$\begin{cases} (2p-1)S + \frac{q_0}{2}(1+tanh(\frac{m-m_0}{\sigma})D = 0, & (14) \\ 2(1-p)S - (d + \frac{q_0}{2}(1+tanh(\frac{m-m_0}{\sigma}))D = 0, & (15) \end{cases}$$

Summing both equations one gets:

$$\cancel{2pS} - S + \cancel{\frac{q_0}{2}(1+tanh(\frac{m-m_0}{\sigma}))D} + 2S - \cancel{2pS} - dD - \cancel{\frac{q_0}{2}(1+tanh(\frac{m-m_0}{\sigma}))D} = 0$$

$$S - dD = 0 \quad \Rightarrow \quad S = dD \tag{16}$$

.2 Coordinates of $\mathcal{F}_1$ and $\mathcal{F}_2$

In the case where $a = 0$ ($\rightarrow a_{1,2} = 0$), system of equations in paragraph 2 becomes:

$$\begin{cases} -S + \frac{q_0}{2}(1+tanh(\frac{m-m_0}{\sigma})D = 0, \\ 2S - (d + \frac{q_0}{2}(1+tanh(\frac{m-m_0}{\sigma})D = 0, \\ 0 = 0, \\ \gamma e^{-\frac{S}{S_0}} - \alpha m = 0 \end{cases} \tag{17}$$

From the fourth equation one straightforwardedly gets the value for S_2:

$$\gamma e^{-\frac{S}{S_0}} - \alpha m = 0 \quad \Rightarrow \quad S = -S_0 \cdot log\Big(\frac{\alpha m}{\gamma}\Big)$$

Since $D = \frac{S}{d}$, as has been proven in Appendix .1:

$$D = -S_0 \cdot log\Big(\frac{\alpha m}{\gamma}\Big)\frac{1}{d}.$$

By plugging $D = \frac{S}{d}$ in the first equation of (17), one gets:

$$\begin{aligned} -\cancel{S} + \frac{q_0}{2}(1+tanh(\frac{m-m_0}{\sigma}))\frac{\cancel{S}}{d} &= 0 \\ \frac{q_0}{2}(1+tanh(\frac{m-m_0}{\sigma})) &= d \\ \frac{m-m_0}{\sigma} &= tanh^{-1}(\frac{2d}{q_0} - 1) \\ m &= \sigma tanh^{-1}(2\frac{d}{q_0} - 1) + m_0. \end{aligned}$$

The logarithm in S and D then distinguishes two different cases: the case for which its argument $\frac{\alpha m_2}{\gamma}$ is equal to 1, and the case $\frac{\alpha m_2}{\gamma}$ where it is generally different from 1. In the former case, the logarithm will vanish carrying with him the values of S and D. This condition will define the so-called first fixed point $\mathcal{F}_1$, with zero concentrations of cancer cells. In the latter case ($\frac{\alpha m_2}{\gamma}$ generally different form 1), the logarithm will generally be non-vanishing, therefore defining non-vanishing values of S and D for the so-called second fixed point $\mathcal{F}_2$.

.3 Coordinates of $\mathcal{F}_3$

The third fixed point $\mathcal{F}_3$ corresponds to the solution of the fixed point equation for which $a \neq 0$:

$$a\Big(\beta S\frac{Sa}{1+a}-\alpha\Big)=0 \quad \Rightarrow \text{if } a\neq 0 \text{ this holds true when: } \Rightarrow \beta S_3\frac{S_3a_3}{1+a_3}-\alpha=0$$

Instead of using the latter condition to express a_3 as a function of S_3, one chooses to use it to define S_3 and D_3 as a function of a_3. One gets:

$$S_3=\frac{\alpha}{\beta}\frac{1+a_3}{a_3} \quad \text{and} \quad D_3=\frac{S_3}{d}=\frac{\alpha}{\beta d}\frac{1+a_3}{a_3}$$

Then, for the following, one must consider that the case $a=0$ corresponded to a zero probability p that cancer stem cells will divide and give birth to one of their kind. Indeed, one recalls that $p=\frac{\eta a}{(1+\eta a)(1+\psi D)}$. But as mentioned above, the division can be either symmetric or asymmetric. p therefore only takes three possible values: $0, \frac{1}{2}$ and 1. The latter value is however not interesting, because it means that no *differentiation* ever happens. The case of the third fixed point will therefore be: $p=\frac{1}{2}$.

$$\begin{aligned}\frac{\eta a_3}{(1+\eta a_3)(1+\psi D_3)}&=\frac{1}{2}\\ 2\eta a_3&=1+\eta a_3+\psi D_3+\psi\eta a_3 D_3\end{aligned}$$

One then plugs the value of D_3 in the latter equation:

$$\begin{aligned}2\eta a_3&=1+\eta a_3+\psi\frac{\alpha}{\beta d}\frac{1+a_3}{a_3}+\psi\eta a_3\frac{\alpha}{\beta d}\frac{1+a_3}{a_3}\\ \eta a_3^2&=a_3+\frac{\psi\alpha}{\beta d}(1+a_3)+\eta\frac{\psi\alpha}{\beta d}a_3(1+a_3)\\ \eta a_3^2&=\frac{\psi\alpha}{\beta d}+(1+\frac{\psi\alpha}{\beta d}(1+\eta))a_3+\eta\frac{\psi\alpha}{\beta d}a_3^2\end{aligned}$$

a_3 must thus satisfy a second order equation:

$$\eta\Big(1-\frac{\psi\alpha}{\beta d}\Big)a_3^2-\Big(1+\frac{\psi\alpha}{\beta d}(1+\eta)\Big)a_3-\frac{\psi\alpha}{\beta d}=0 \tag{18}$$

Solutions are:

$$a_3=\frac{1}{2}\frac{1+\frac{\Psi\alpha}{d\beta}(1+\eta)}{\eta(1-\frac{\Psi\alpha}{d\beta})}\Big(1\pm\sqrt{1+\frac{4\frac{\Psi\alpha}{d\beta}\eta(1-\frac{\Psi\alpha}{d\beta}))}{(1+\frac{\Psi\alpha}{d\beta}(1+\eta))^2}}\Big)$$

Since, for the existence of this third fixed point one requires that $d > \frac{\psi\alpha}{\beta}$, i.e. $\frac{\psi\alpha}{d\beta} < 1$, the solution with the minus sign would be unphysical, as it would give a negative value for a_3. Hence:

$$a_3 = \frac{1}{2}\frac{1+\frac{\Psi\alpha}{d\beta}(1+\eta)}{\eta(1-\frac{\Psi\alpha}{d\beta})}\Big(1+\sqrt{1+\frac{4\frac{\Psi\alpha}{d\beta}\eta(1-\frac{\Psi\alpha}{d\beta}))}{(1+\frac{\Psi\alpha}{d\beta}(1+\eta))^2}}\Big)$$

.4 Stability of $\mathcal{F}_1$ - Analytically

The Jacobian in eq. 8 evaluated at $\mathcal{F}_1$ reads:

$$\begin{pmatrix} -1 & q(m) & 0 & 0 \\ 2 & -(d+q(m)) & 0 & 0 \\ 0 & 0 & -\alpha & 0 \\ -\frac{\gamma}{S_0} & 0 & 0 & -\alpha, \end{pmatrix}$$

Two eigenvalues are trivially $\lambda_{1,2} = -\alpha$. It is then sufficient to compute the characteristic polynomial of the following sub-matrix:

$$\begin{pmatrix} -1 & q(m) \\ 2 & -(d+q(m)) \end{pmatrix}$$

The characteristic polynomial will look like:

$$\lambda^2 + (1+d+q(m))\lambda + d - q(m) = 0$$

Its roots give the remaining eigenvalues:

$$\lambda_{3,4} = \frac{1}{2}\Big(-(1+d+q(m)) \pm \sqrt{(1+d+q(m))^2 - 4(d-q(m))}\Big)$$

Since parameters are assumed to be all positive, the four eigenvalues of $\mathcal{F}_1$ are negative as long as:

$$\sqrt{(1+d+q(m))^2 - 4(d-q(m))} < (1+d+q(m)) \Rightarrow d > q(m)$$

However, since q_0 is the maximum value that $q(m)$ can take, condition $d > q_0$ implies that $d > q(m)$. In conclusion, all eigenvalues are negative -and $\mathcal{F}_1$ is attractive- if $d > q_0$. On the contrary, one of the eigenvalues may be positive, if $d < q_0$. In that case, $\mathcal{F}_1$ will be saddle.

.5 Stability of $\mathcal{F}_2$ - Analytically

The Jacobian in eq. 8 evaluated in the second fixed point reads:

$$\begin{pmatrix} -1 & d & \frac{2S_2\eta}{1+\psi D_2} & \frac{2dD_2}{\sigma}\Big(1-\frac{d}{q_0}\Big) \\ 2 & -2d & -\frac{2S_2\eta}{1+\psi D_2} & -\frac{2dD_2}{\sigma}\Big(1-\frac{d}{q_0}\Big) \\ 0 & 0 & -\alpha & 0 \\ -\frac{\alpha m_2}{S_0} & 0 & 0 & -\alpha, \end{pmatrix}$$

The third line of the Jacobian clearly shows that one eigenvalue is $\lambda_1 = -\alpha$. It is then sufficient to compute the characteristic polynomial of the following sub-matrix:

$$\begin{pmatrix} -1 & d & \frac{2dD_2}{\sigma}\Big(1-\frac{d}{q_0}\Big) \\ 2 & -2d & -\frac{2dD_2}{\sigma}\Big(1-\frac{d}{q_0}\Big) \\ -\frac{\alpha m_2}{S_0} & 0 & -\alpha, \end{pmatrix}$$

The equation to be solved in order to determine the eigenvalues will be the following:

$$\lambda^3 + (\alpha + 1 + 2d)\lambda^2 + (\alpha(1 + 2d) - B)\lambda - Bd = 0,$$

where $B = \frac{2\alpha}{\sigma}(1 - \frac{d}{q_0})log(\frac{\alpha m_2}{\gamma}) \times m_2$. As a consequence of the conditions for the existence of this second fixed point, one can state that B is negative, whatever the values of the parameters. Indeed, $m_2 < \frac{\gamma}{\alpha}$ implies that the logarithm in B will be negative ; and $d < q_0$ implies that the part into brackets will always be positive. B being negative, all the coefficients in the characteristic polynomial will be positive. The Routh-Hurwitz result [12] states that for a characteristic polynomial of the form $\lambda^3 + p\lambda^2 + q\lambda + r = 0$, where $p, q, r > 0$, which is precisely the present case, the three roots will have a negative real part as long as $p \times q > r$ [5]. As a consequence, the second fixed point will be attractive as long as:

$$(\alpha + 1 + 2d)(\alpha(1 + 2d) - B) > -Bd$$
$$\frac{1}{q_0} \cdot (\alpha + 1 + 2d) \cdot (\alpha(1 + 2d) - B) > -B \cdot \frac{d}{q_0}$$

However this inequality is always satisfied for $d < q_0$. Indeed, this condition for the existence of $\mathcal{F}_2$ gives an upper bound for the right-hand-side: $-B \cdot \frac{d}{q_0} < -B \times 1$. One therefore gets:

$$\frac{1}{q_0} \cdot (\alpha + 1 + 2d) \cdot (\alpha(1 + 2d) - B) > -B$$
$$\alpha^2(1 + 2d) - \alpha B + \alpha(1 + 2d) - \cancel{B} + 2\alpha d(1 + 2d) - 2dB > -\cancel{B}$$
$$\alpha^2(1 + 2d) - \alpha B + \alpha(1 + 2d) + 2\alpha d(1 + 2d) - 2dB > 0 \quad \Rightarrow \quad \text{always true for } B < 0$$

.6 Stability of $\mathcal{F}_3$ - Analytically

The Jacobian (eq. 8) evaluated in $\mathcal{F}_3$, with $q(m_3) = 0$, $p = \frac{1}{2}$ and $S_3 >> S_0$, simplifies to:

$$\begin{pmatrix} 0 & -d\tau\frac{\psi_0}{2\eta} & \frac{\tau\alpha}{\beta(1+\eta a_3)^2} & \frac{\partial q}{\partial m}(m_3) \cdot D_3 \\ 1 & d\tau\frac{\psi_0}{2\eta} - d & -\frac{\tau\alpha}{\beta(1+\eta a_3)^2} & -\frac{\partial q}{\partial m}(m_3) \cdot D_3 \\ \frac{\beta a_3^2}{1+a_3} & 0 & \frac{\alpha}{1+a_3} & 0 \\ 0 & 0 & 0 & -\alpha, \end{pmatrix}$$

where $\tau = \frac{(1+a_3)(1+\eta a_3)}{a_3^2}$ and $\frac{\partial q}{\partial m}(m_3) = \frac{q_0}{\sigma}(1 + tanh(\frac{m_3 - m_0}{\sigma}))\Big[1 - \frac{1}{2}(1 + tanh(\frac{m_3 - m_0}{\sigma}))\Big]$. This form of the Jacobian can be proven by taking into account the fact that for $\mathcal{F}_3$, the following equation holds:

$$\frac{\psi\alpha}{d\beta} = \frac{a_3(\eta a_3 - 1)}{(1 + a_3)(1 + \eta a_3}),$$

which was obtained by solving eq. 18.

One trivially has that $\lambda_1 = -\alpha$. The three remaining eigenvalues will be given by the following characteristic polynomial:

$$
\begin{aligned}
0 &= \lambda^3 + A \cdot \lambda^2 + B \cdot \lambda + C \\
A &= d - \frac{\alpha}{1 + a_3} - \frac{\tau\psi\alpha}{2\beta\eta} \\
B &= -\alpha\Big(\frac{1}{1 + \eta a_3} + \frac{d}{1 + a_3}\Big) + \frac{\psi\alpha}{2\eta\beta a_3^2}(1 + a_3 + \alpha)(1 + \eta a_3) \\
C &= -\alpha d\Big(\frac{1}{1 + \eta a_3} + \frac{(1 + \eta a_3)\psi\alpha}{2\eta\beta a_3^2}\Big)
\end{aligned}
$$

One sees that C is always negative. Moreover, since $C = -\lambda_2 \cdot \lambda_3 \cdot \lambda_4$, the product of the three remaining eigenvalues will be positive ($\lambda_2 \cdot \lambda_3 \cdot \lambda_4 > 0$) implying that there is always at least one positive eigenvalue. The third fixed point is therefore saddle.

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