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DESIGNING PROLIFERATING CELL POPULATION MODELS WITH FUNCTIONAL TARGETS FOR CONTROL BY ANTI-CANCER DRUGS

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ABSTRACT. We review the main types of mathematical models that have been designed to represent and predict the evolution of a cell population under the action of anti-cancer drugs that are in use in the clinic, with effects on healthy and cancer tissue growth, which from a cell functional point of view are classically divided between "proliferation, death and differentiation". We focus here on the choices of the drug targets in these models, aiming at showing that they must be linked in each case to a given therapeutic application. We recall some analytical results that have been obtained in using models of proliferation in cell populations with control in recent years. We present some simulations performed when no theoretical result is available and we state some open problems. In view of clinical applications, we propose possible ways to design optimal therapeutic strategies by using combinations of drugs, cytotoxic, cytostatic, or redifferentiating agents, depending on the type of cancer considered, acting on different targets at the level of cell populations.

1. **Introduction.** Mathematical models have been called for some time already by cancer biologists and clinical oncologists to help improve the efficacy of anti-cancer treatments. Indeed, understanding better the evolution of cancers and how to treat them in an optimal way is still an open question, that might benefit from contributions of mathematics to represent cell proliferation control by drugs.

Knowing that most anti-cancer treatments use combinations of drugs with different molecular targets and different functional effects on proliferating cell populations, we advocate considering these effects not just as on inhibition of a global 'birth minus death' rate, but rather with a refined point of view, considering multiple targets, representing differential drug effects on birth, death or differentiation, by different control targets in mathematical models. The closer these model representations are to actual clinical questions, the better.

The main two pitfalls of clinical oncology, that limit increasing drug doses, are unwanted toxic side effects on healthy cell populations and occurrence of resistance to drugs in cancer cell populations. According to the medical questions at stake, one may consider different models to represent the underlying biological phenomena that are the object of control by drugs. Spatial representations may be partly helpful, in particular when tumour neo-angiogenesis and anti-angiogenic drugs are present. However, in as much as drug effects are the tools of control considered here, and since they act mostly by modifying the physiology of cells, physiologically structured models should always be used, with or without added spatial structure. In particular, focus will be set here on models structured

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according to age in the cell cycle, or according to an evolutionary phenotype if evolution towards drug resistance is the main issue.

The paper is organised in the following way: firstly, we review the main difficulties inherent to cell population modelling for drug delivery control, and categories of drugs used in the clinic, from a pharmacological point of view. We then present in an abstract way, but with concrete instances, how anti-cancer drug targets may actually be represented in cell proliferation dynamic models. Finally, we briefly review the main types of models lately used in the scientific literature on drug control in healthy and cancer cell populations, sketching some results recently obtained, either theorems, or hints to possible future results coming from mere simulations, when proper mathematical analyses still seem out of reach.

2. Anticancer drug effects and their representation in mathematical models.

The types of models used to predict cell population behaviour under control by drugs range from cellular automata to ordinary and partial differential equations (ODEs and PDEs), PDEs being amenable to transformation into delay differential equations (DDEs) by integration of PDEs along characteristics [42, 72]. Biological variability (physiological differences between cells) is easily taken into account by stochastic models, and so-called individual-based models (IBMs) are amenable to include any kind of rule one puts in the individual agents. These models are hardly amenable to mathematical analysis, in particular to the study of their asymptotics, given the intrinsically finite number of cells they take into account, but their simulation may give hints to possible properties of their behaviour, that need to be further explored by mathematical analysis [28]. As regards physiologically structured PDEs, their structure variables (e.g., age in cell cycle models) electively represent biological variabilities considered as the most relevant for the question at stake, and their asymptotics can be studied when the model is tractable, sometimes resulting in theorems - which is hardly possible with agent-based models.

2.1. Modelling, what to do? Guidelines to design a model for an application.

It should be stressed that designing cell population models under the action of drugs puts from the beginning modellers in a perspective completely different from the one used to represent the “natural history” of tumour growth under the influence of mechanical or physiological factors, but without built-in drug control. Moreover, given the complexity of biological phenomena underlying tissue growth, i.e., proliferation of histologically homogeneous cell populations (notwithstanding some biological variability between individual cells), choosing well delineated questions of therapeutics arising in the clinic of cancers as a source of inspiration helps designing practical models adapted to represent actual treatments, with the aim to answer questions (about prediction of unwanted toxic side effects, drug resistance, and optimal combinations of drugs) asked by clinicians.

Optimisation of drug delivery is always a concern for clinicians. This for mathematicians implies defining an objective function, usually the number or density of cancer cells to be minimised, under constraints that may be limitation of toxicity to healthy cells or avoidance of the thriving of a drug-resistant subpopulation in cancer cells, or both. Oncologists seldom use only one drug, but rather, combinations of drugs acting on different molecular targets with the aim to potentiate their effects. If one wants to accurately represent and study such combinations, it is necessary to design models with built-in specific targets for the drugs in use [31].

Anticancer drugs are most often known for their *molecular* effects, i.e., effects that involve blockade or re-establishment of an intracellular signalling pathway, for instance targeting a specific enzyme or a chain of molecular reactions starting with a membrane or cytosol receptor. Nevertheless, such effects are not always specific, and even when a

drug has been designed to block a given pathway by conformational analysis of known molecules, unexpected other effects may be unravelled by preclinical and clinical trials, and these effects may be deleterious on other pathways or to other cells. Furthermore, anti-cancer drugs show their therapeutic effects in a measurable way only at the cell population level by actual *cell functional* effects, i.e., on cell death, birth or differentiation.

This points out the multiscale nature of drug delivery problems: drugs are given at the whole body level (collection of communicating cell populations), exert their effects at the single cell level, but these effects, as far proliferation is concerned, are actually measurable at the cell population level only [32]. The most relevant level to describe proliferation and its control by drugs is clearly the cell population level, but the single cell (molecular, at which drugs chemically act) and whole body (at which drugs at delivered) levels must also be considered, at least if one aims at designing models for practical applications, i.e., for therapeutic optimisation. Drug effects must be different in cancer and in healthy cell populations if a therapeutic benefit is searched for, which stresses the fact that identical functional targets should be represented as behaving differently in cancer and in healthy tissues.

Note that we will consider here only *proliferating* cell populations. In an extended representation including applications to fast invading tumours (e.g., gliomas) and their treatments, a fourth fate for tumours beyond cell proliferation, death and differentiation that should be considered is cell motion, which ("go or grow" alternative) is, in a given time lapse, incompatible with proliferation [29].

2.2. **A level gap between molecular and functional targets.** Anticancer drugs that are designed for their effects at the molecular level are most often known to block a specific intracellular signalling pathway (a chain of molecular reactions) that is assumed to end up by being involved in "apoptosis, proliferation, differentiation" all together, with seldom further precisions, because of the entanglement of the various molecular pathways participating in these physiological cell functions. Molecules designed at the single cell level thus need to be further studied at upper levels, by cell population dynamic studies in cell cultures and in experimental animal models, to investigate in a differential way all these physiological functions, plus drug resistance in diseased cell populations.

Otherwise said, in the same way as silencing a gene may have effects on other phenotypes than the targeted one, blocking a molecular pathway has seldom specific effects on a functional target in a cell population, hence the interest of investigating combinations of drugs by their functional more than by their molecular effects, and at the cell population rather than at the molecular level, from an experimental point of view in cell cultures. Such process obviously ought to be completed by further studies using whole body animal experiments, to unravel possible unexpected toxic side effects on other cell populations, possibly resulting in prohibitive toxicities to healthy tissues.

The gap to bridge between these three levels of observation (single cell, cell population, whole body) of this multiscale perspective is an intrinsic difficulty for which no miracle solution is known in general. Specific ways to integrate them depend on the type of model used at the cell population level, which is central in proliferation. A common suggestion [31, 32] is to use compartmental ODEs for pharmacology (pharmacokinetics-pharmacodynamics, PK-PD for short) of anti-cancer drugs, structured PDEs for cell populations in each compartment, and a simultaneous management of the cell populations attacked by drugs by optimisation algorithms at the whole body level.

2.3. **Drugs used in cancer treatments considered at the single cell level.** Tissue renewal, which at the cell population level is made of proliferation, cell death and differentiation, relies on physiological phenomena that are built of elementary molecular reaction chains, and it is on these cell biochemical reactions that anti-cancer drugs act. In particular, proliferation of cell populations relies at the single cell level on the cell division cycle [60].

2.3.1. *DNA damaging agents.* Also known as alkylating agents, these drugs act by directly binding to the DNA and creating damages in it, such as double strand breaks, that are hard to repair by the cell. They are in principle not cell cycle phase-specific. However, the fact that DNA is less protected in S phase, when it is duplicated, makes them more active in this phase. Commonly used alkylating agents are for instance cisplatin, oxaliplatin and cyclophosphamide. DNA damaging agents are cytotoxic drugs (see below).

2.3.2. *Cell cycle phase-specific agents.* S phase-specific drugs block DNA replication either by acting as substrate substitutes in metabolic reactions (antimetabolites) or by inhibiting enzymes of these metabolic reactions, or both. Such are 5-Fluorouracil, a substitute for normal uracil, that also acts by blocking the enzyme thymidilate synthase, and irinotecan, that blocks topoisomerase II, an enzyme that is essential to DNA replication. M phase specific drugs block mitosis either by destroying the mitotic spindle (spindle poisons, such as vinca alkaloids, e.g., vincristine) or preventing its dissociation, such as taxanes (e.g., docetaxel and taxotere). These drugs secondarily create damages to the DNA (and thus are cytotoxic) since it cannot be properly duplicated (S phase-specific drugs) or they produce cells that are unable to divide; in both cases, cells under attack are short-lived due to cell control mechanisms occurring at so-called checkpoints (see below *Cell death*).

2.3.3. *Molecular targeted therapies.* Although in principle all drugs have molecular targets, that are defined as specifically as possible, this recently denominated category of drugs was firstly restricted to chemicals shown to very specifically re-establish the normal functioning of a molecular signalling pathway perturbed in cancer. One of the first used molecular targeted therapies was in 1986 all-transretinoic acid or ATRA, a molecule that corrects the normal granulocyte differentiation process blocked in acute promyelocytic leukaemia (APL, also known as type 3 acute myeloblastic leukaemia) by the chimeric protein PML-RARα, ATRA destroying this protein [45]. The term 'molecular targeted therapy' now includes mostly monoclonal antibodies (associations of a growth factor receptor antagonist with an antibody that is specific of the receptor, with a name usually ending in -mab) and tyrosine kinase inhibitors (TKIs, that directly block growth factor receptors in kinases at a tyrosine site, with a name usually ending in -nib). The best known success story in molecular targeted therapies is that of imatinib mesylate, that has completely transformed the prognosis of chronic myelogenous leukaemia (CML) [40]. ATRA and imatinib actually cure most of APL (over 80%, by using it in combination with a cytotoxic drug) and CML (over 95%, in monotherapy) patients, respectively, likely because they are directed against well identified chimeric (abnormal) proteins, PML-RARα and BCR-Abl, respectively. However, in cases where other protein targets are normal but only abnormally overexpressed, molecular targeted therapies are not so effective, and sometimes highly toxic. Other recent molecular targeted therapies include histone deacetylase (HDAC) inhibitors, drugs that block the effects of HDACs, electively in cancer cells, since healthy cells seem to be more protected against their effects. Since these enzymes are involved in most cell processes (proliferation, cell differentiation and death), they may be molecule-specific, but not functionally specific, as are for instance imatinib on proliferation or ATRA on differentiation; however, tentative functional distinctions between them have been proposed [85].

Molecular targeted therapies are usually cytostatic (see below) but may become cytotoxic at high doses.

2.4. **Drug effects and targets at the cell population level.** Indeed, since the aimed-at and clinically measurable effects of drugs are functional (on proliferation, cell differentiation or death) at the cell population level, it is at least as interesting to consider such drug effects as acting on functional terms in model equations representing tissue growth. As mentioned above, bridging the gap between the molecular and functional effects of anti-cancer drugs remains in general an open question. Another issue in the measurement of drug effects in cell populations comes from technological limitations due to the tools used to identify model parameters, that seldom can be all highlighted, unless the model is very simplified. Such identification relies in particular on flow cytometer measurements [79, 80] and, more recently, on fluorescence-based methods investigating cell by cell a whole population [23, 74, 75].

2.4.1. *Cytotoxics and cytostatics.* Cytotoxic drugs are those that are aimed at killing cells - usually killing not only cancer cells -, sending them to death either by directly launching apoptosis (i.e., 'clean' cell death), or blocking them in an irreversible phase of the division cycle where long-term survival is impossible. On the contrary, cytostatic drugs may kill not even a single cell, being not directed at creating damages to the cells, but rather slow down the growth of the cell population as a whole, which may be experimentally evidenced by a lengthening of the cell population doubling time. It is known however that, depending on the drug dose, various cytostatics may become cytotoxic, and this has been represented in a model dealing with lapatinib [47].

2.4.2. *Cell death.* A direct enhancement of death rates by drugs is the simplest way to represent the effect of cytotoxics, and it is the only one available in the simplest ODE models where a *"birth minus death"* term is the only possible target in the equations (i.e., $\frac{dn}{dt} = r(n).n - d.n$). Although apoptosis pathways, involving at the molecular level members of the Bcl2 family, have been explored with the aim to find targets for drugs that would be specific of apoptosis launching, it does not seem that specific proapoptotic drugs are already routinely available in the clinic. However, if one wants to oppose drug effects that are clearly cytotoxic to others that are only cytostatic, it is licit, provided that the model allows separate identifiability of cytotoxic and cytostatic effects, to represent cytotoxic effects on death rates, as opposed to cytostatic ones on proliferation rates.

In age-structured models of the cell division cycle, where cell cycle phases are distinct, separated by transition rates between them, it is also possible, knowing that these transitions are under the control of protein p53 - "the guardian of the genome" -, itself triggered by DNA damage, to represent cytotoxic effects, rather than directly on death rates, by p53-mediated blockade of the cell cycle at these transitions (so-called checkpoints, mainly between G_1 and S, and between G_2 and M phases). We allude here at McKendrick-like PDE models for the density $n_i(t,x) \geq 0$ of cells with age x in cell cycle phase $i = 1, \ldots, I$ at time t, in which inputs of drug may be considered as impacting death terms $d_i(t,x)$ in phases or boundary terms, p53-controlled transition rates $K_{i\to i+1}(t,x)$ between phases in transport equations for cell division cycle phases

$$\frac{\partial}{\partial t} n_i(t,x) + \frac{\partial}{\partial x}\{v_i(x) n_i(t,x)\} + \{d_i(t,x) + K_{i\to i+1}(t,x)\} n_i(t,x) = 0 \qquad (1)$$

with boundary terms $n_i(t, x = 0) = \int_{\xi \geq 0} K_{i-1\to i}(t,\xi)\ n_{i-1}(t,\xi)\ d\xi$. (See below Eq. (5) for a more complete description.)

But then one would have to describe in equations the actual sequencing of physiological mechanisms by which, as classically stated in biology tutorials, p53 arrests the cell cycle and launches DNA repair or apoptosis [81], subsequently relating by complementary equations the d_i to the $K_{i\to i+1}$, i.e., how should cell death launch be represented when cells have spent "too much time" blocked at checkpoints? This is a task that to our knowledge has not been done thus far, essentially because of lacking physiological knowledge on the timing in this sequence of events. Likely, cell energetic considerations (e.g., on ATP consumption) could be helpful. Nevertheless, cell death at check points can be mimicked in a coarse way in numeric simulations by imposing an arbitrary maximum number of runs of the division cycle for a given cell until it passes to next phase.

Furthermore, enzymatic repair mechanisms (nucleotide excision repair, NER, after damage to the DNA) are important to consider since resistance to anti-cancer drugs may be due their over-expression (and it is also the only way to explain resistance to radiotherapy). Thus they should also be included in a model of control of proliferation to complete the representation of this p53-related missing link between DNA damage induced by cytotoxic drugs and its consequences on death rates at the cell population level. This also remains to be done, to our knowledge.

2.4.3. *Proliferation terms: birth rate or ageing speed.* Effects of cytostatic drugs, that slow down proliferation without destroying cells, may be represented in simple models by a decrease in a multiplicative growth factor affecting the cell population variable, e.g., by introducing a drug effect f in an equation of the form

$$\frac{dn}{dt} = \frac{r(n).n}{1+f(t)} - d.n, \tag{2}$$

which obviously does not distinguish them, in this simple form, from additive effects on death rates. But they may be represented in different and richer ways in models of the cell division cycle, such as constituted of copies of the McKendrick equation presented above, and also below in a more detailed way, see Eq. (5), by an inhibiting action on the speed v_i with which phase i (mostly G_1 or G_2) is scrolled through, or by introducing an inhibiting factor before the boundary terms $\displaystyle\int_{\xi\geq 0} K_{i\to i+1}(t,\xi)\ n_i(t,\xi)\ d\xi$, both ways to mean a negative effect on the influence of growth factors, which usually is the result of the action of cytostatic drugs.

2.4.4. *Sending cells to quiescence.* Another way to represent the effect of cytostatic drugs is to use age-structured models in which cell cycle phases are not necessarily detailed, keeping only one proliferative phase, but introducing exchanges of proliferating cells with a quiescent phase in which cells do not grow. One may thus represent cytostatic effects by a contrasted fate at mitosis, sending proliferating cells with density $p(t,x)$ either back into the division cycle, or to a storage siding Q representing a quiescent phase, as in [43], depending on the cytostatic drug-controlled factor f (see below Eq. (6)). Such a model is still linear and thus amenable to asymptotic analysis by investigating its first eigenvalue, or Malthus exponent [72]. But it would be also possible to perform the same representation of drug effects on exchanges between proliferation and quiescence in non linear models involving furthermore feedback from quiescence onto proliferating cell populations, following models for stem cell populations as proposed by Mackey in a delay-differential form in 1978 [55], and later by many others, in particular [19, 20, 39] in a PDE form with both age and molecular structure, further studied with reduction to the only molecular (cyclin D) structure in [25, 26]. It is also possible in these models to linearise the system around stationary points (zero or infinite total cell population) to perform asymptotic analyses.

2.4.5. *Differentiation terms.* The same kind of models, applied to haematopoietic cell populations, for which cell differentiation is relatively well known and in which it is completely blocked at different maturation stages in acute myelobloblastic leukaemia (AML), in particular at the promyelocytic stage mentioned above about APL, has been studied by Adimy *et al.* They proposed a model with continuous age and discrete maturity structure [1], for which a stability analysis was performed and stability conditions involving both proliferation and differentiation, are given[67, 68]. In its delay-differential version (obtained by integration in age along characteristics [42, 72]), the model describes at each maturation stage i the dynamics of both quiescent and proliferating cells, as in Mackey's models [42, 55], see below 'Extension to delay differential models'.

2.4.6. *Exploring alternative ways.* Representing drug effects in cell populations yielding acquired resistance by Darwinian-like phenomena makes one consider populations structured according to a continuous resistance phenotype x rather than to an age variable. Such models, that are widespread in the ecological modelling community, are only beginning to diffuse in the cancer biological modelling world. They may involve mutations, competition and feedback from the environment, as presented in a general way in [54].

Furthermore, these models are also well adapted to represent, by using environmental variables such as pH and intercellular signalling molecules (e.g., cytokines), the influence of energetic and metabolic settings, that are assumed to play a role in pharmacotherapeutics, in particular when one considers involvement of the immune system, as in [37].

3. **Short review of cell population models with targets for drug effects.** In this section, we present a brief review of various types of models that have been designed to investigate drug efficacy on cancer cell populations. A lot of work has been performed in this domain since the end of the 20th century, and we do not claim here to be exhaustive, but only sketch the scenery by choosing examples. More can be found in [22], where the presentation is focused on drug delivery optimisation, and in the synoptic [76] and in the references in these articles. We focus here on the representation of drug targets in these models.

3.1. **Cellular Automata.** A popular way among physicists, chemists and biologists to represent the cell division cycle is to consider this cycle as a set of prescribed biological rules that govern cell evolution. In this way, cellular automata enable to describe individual cell evolution within a cell population and to investigate drug efficacy.

Altinok and Goldbeter developed a cellular automaton for the cell cycle [4, 5, 6, 7]. Transition between two states of the automaton, that represent phases of the cell cycle, correspond to cell progression through, or exit from, the cell cycle, and are assumed to respect some prescribed rules. For instance each phase of the cell cycle is assumed to be characterised by a mean duration and a variability in order to take into account inter-cell variability that can appear within a population. This cellular automaton was coupled with a model of the circadian clock in order to investigate the cytotoxic effects of time-scheduled (delivered according to a periodic schedule) infusions of 5-fluorouracil (5-FU) [5, 6]. The authors modelled the effects of 5-FU on the cell cycle by increasing the probability that cells submitted to this drug while in S phase exit from the cell cycle at the next G_2/M transition. Altinok *et al.* also investigated the effects of oxaliplatin time-scheduled therapies on cancer cells [7]. Contrary to 5-FU, oxaliplatin is an anti-cancer agent that is not phase-specific. Therefore the authors modelled the effects of oxaliplatin on the cell cycle progression by increasing the probability for exposed cells of exiting the cycle at the next checkpoint (G_1/S or G_2/M transitions).

3.2. **Ordinary Differential Equations.** The most popular models that formed the basis of the development of models to investigate drug efficacy are the exponential model ($\frac{dn}{dt} = \lambda n$), the logistic ($\frac{dn}{dt} = \lambda n \left(1 - \frac{n}{K}\right)$, where K is the maximum tumour size, or "carrying capacity" of the environment), and the Gompertz ($\frac{dn}{dt} = \lambda n \ln\left(\frac{K}{n}\right)$, where again K is the carrying capacity). A lot of studies on drug control are based on these models [12, 13, 30, 56, 57, 58, 61, 62, 63]. To model the action of cytotoxic drugs, these models integrate a cell loss term that depends on the drug concentration and that can be generically written as:

$$\frac{dn}{dt} = \lambda n \ln\left(\frac{K}{n}\right) - L(n, D) \tag{3}$$

where $L : \mathbb{R}^2 \to \mathbb{R}$ is a function, not necessarily linear, of the density of cells N and of the drug concentration D. The drug concentration D is usually given as the solution of an ODE that depends on the drug infusion rate and that can be seen as the output of a more or less complicated PK-PD model. For instance, Martin [56] developed such a model with a function L linear in n and D to optimise chemotherapy schedules under constraints of maximal tolerated doses. In a more mechanistic way, Barbolosi and Illiadis [12] defined the drug concentration thanks to a two-compartment model of the chemotherapy PK.

These models consider only one cell population, whereas others integrate several kinds of cell populations. Distinguishing between tumour cell and healthy cell populations enables to take into account possible side-effects of the treatment on the population of normal cells [13, 30, 61, 62]. For instance, in [13] Basdevant *et al.* proposed two optimisation problems. The first one consisted in determining the drug infusion scheme that would minimise the number of tumour cells while kipping the number of healthy cells above a given threshold. The second one consisted in finding a quasi-periodic drug infusion scheme that would maintain the tumour cell population at the lowest possible level while preserving the healthy cell population. As tumour cell resistance can be responsible for the failure of chemotherapy, Martin *et al.* [58] considered two tumour cell subpopulations: one sensitive to treatment and the other one insensitive to treatment. They assumed that sensitive tumour cells could spontaneously become insensitive and that chemotherapy had a cytotoxic effect only on sensitive cells. In another work [57], the same authors studied the effect of a combination of two chemotherapies and thus considered three cell subpopulations, differentiating cells being insensitive to one of the two chemotherapies or to both chemotherapies.

To design a more realistic model of tumour growth, in particular to study the effects of anti-angiogenic agents on tumour growth, Hahnfeldt [46] considered, in a Gompertz model, the carrying capacity K as a variable. The variations of this carrying capacity were given by an ODE integrating the spontaneous, the tumour-induced and the anti-angiogenic drug-induced vasculature loss. More recently, some authors based themselves on this approach to study other kinds of variations for the carrying capacity K and to analyse the effect of anti-angiogenic therapies combined with chemotherapies or radiotherapies [41, 52, 64, 65, 66]. For instance, in [52], Ledzewicz *et al.* analysed an optimisation problem that consisted in minimising the final volume of a tumour submitted to a combination of an anti-angiogenic and a cytotoxic anti-cancer treatment, under constraints on the total amounts of the two drugs. This study enabled the authors to propose optimal infusion schemes for such combination of anti-cancer agents.

Most anti-cancer agents are phase-specific, which means that they target only cells that are in a specific phase of the cell division cycle. To analyse the effect of such chemotherapies on cancer cell populations, models that integrate two or more compartments representing the phases or additions of the phases of the cell cycle have been developed. The simplest ones distinguish between cycling and non-cycling cells and suppose that only cycling cells are sensitive to chemotherapy through a death term [69, 70, 83, 84]. Other more detailed models combine for instance G_1 and S phases in one compartment and G_2 and M in another one [50, 77], or consider the phases G_0 and/or S in separate compartments [71]. These models aim at accounting for the effects on cancer cell populations of phase-specific chemotherapies, that can be cytotoxic or cytostatic. For instance, Kozusko et al. [50] analysed the effects on cell cycle progression and cell viability of several doses of curacin A by representing its effects on the transition rates between phases G_1 and S, and between G_2 and M of the cell division cycle, and on cell apoptosis rate, cells being distinguished between sensitive and resistant cells. Panetta *et al.* [71] then completed this model by separating the phases G_1 and S in order to investigate the effects of 6-mercaptopurine, an S phase-specific drug, on the dynamics of the cell cycle in populations of cells that were more or less resistant to the treatment. Swierniak *et al.* [77, 78] distinguished between G_0, G_1, and $S/G_2/M$ to analyse the effects of a cytotoxic chemotherapy combined with 'recruiting' agents such as cytokines, that enable the global cell population to recruit cells from the quiescent phase G_0 into the proliferating phase, which is assumed to make then sensitive to the cytotoxic treatment, i.e., to subsequently kill them when they are definitely committed in the cell cycle.

3.3. **Partial Differential Equations: physiologically structured transport equations.** Cell population growth also depends on the physiological properties of cells. Such physiological properties can be age of the cells (i.e., the time elapsed since the last cell division), mass or volume of the cells, their degree of resistance to treatment, their DNA content, the size of the induced metastases, etc. To take into account in a population of cells between-individual variability linked to these physiological parameters, the McKendrick (or Von Foerster-McKendrick) PDE framework is particularly well suited:

$$\begin{cases} \dfrac{\partial n}{\partial t}(x,t) + \dfrac{\partial}{\partial x}\{v(x)n(x,t)\} + d(x)n(x,t) = 0 & (t>0, x>x_{min}) \ , \\ n(x_{min},t) = \displaystyle\int_{x_{min}}^{\infty} \beta(\xi)n(\xi,t)\, d\xi & (t>0) \ , \\ n(x,0) = n_0(x) & (x>x_{min}) \ , \end{cases} \tag{4}$$

where $n(x,t)$ is the density of proliferating cells with characteristic x (age, mass, volume, DNA content, etc.) at time t, v is the cell growth rate (a velocity relating physiological characteristic x to time t), d is the death rate, β is the birth rate, $x_{min} \geq 0$ is the minimum value of x for a cell to actually proceed in the cycle. Note that v, d, β depend on x.

The McKendrick model is positive and linear, and as such its asymptotics is governed by a first eigenvalue λ, also called *Malthus exponent*. It can be proved indeed (using the Krein-Rutman theorem and a generalised relative entropy - GRE - principle, see, e.g., [72]) that its solution may be represented for large times t by a bounded function times $exp(-\lambda t)$.

Physiologically structured cell population dynamics models have been extensively studied in the last 25 years, see e.g., [8, 9, 10, 11, 17, 18, 21, 23, 33, 34, 44, 47, 48, 49, 59, 73, 82]. We focus here, as mentioned earlier, on those that explicitly include a target for the representation of drug effects to control their dynamics.

3.3.1. *Age-structured models for the cell division cycle.* Age of cells in the cell cycle is one of the the most used physiological characteristics in the literature on physiologically structured models. The main interest of considering an age-structured model is in distinguishing, in a representation of the cell division cycle, between physiological time (age) and external time, in the perspective of controlling the cycle by drugs that act on it, as do most anti-cancer drugs.

In the McKendrick model, the variable a corresponds to the age of the cells in the cell division cycle for a one-compartmental model (cf Eq. (4)), or more generally to the age of the cells in each of the I phases (or addition of phases, e.g., S and G_2, or G_2 and M) of the cell cycle:

$$\begin{cases} \dfrac{\partial}{\partial t} n_i(t,x) + \dfrac{\partial}{\partial x}\{v_i(x)\ n_i(t,x)\} + \{d_i(t,x) + K_{i\to i+1}(t,x)\}\ n_i(t,x) = 0 \ , \\ n_i(t,x=0) = \displaystyle\int_{\xi\geq 0} K_{i-1\to i}(t,\xi)\ n_{i-1}(t,\xi)\ d\xi \quad 2 \leq i \leq I \ , \\ n_1(t,x=0) = 2\displaystyle\int_{\xi\geq 0} K_{I\to 1}(t,\xi)\ n_I(t,\xi)\ d\xi \ , \end{cases} \tag{5}$$

in which protein p53 is assumed to control phase transition kernels $K_{i\to i+1}$ between phases i and $i+1$, e.g., G_1 and S.

As in the case of ODE models, the simplest way to represent the action of a cytotoxic treatment is to enhance the death rate of the cell population according to the treatment activity. Thus Kheifetz *et al.* [49] used a one-compartment age-structured cell cycle model where the death rate integrates the drug activity through an exponentially decreasing multiplicative function.

As mentioned earlier, age-structured models have also been used to represent the action of cytotoxic agents by their effects, not directly on death rates, but primarily on phase transition rates, death occurring only secondarily, when cells have been blocked long enough at phase transition checkpoints. In [23, 33, 34], the authors consider a multiphase age-structured PDE model of the cell cycle in which is introduced a time dependency of the parameters (death rate, transition rate from one phase of the cell cycle to the next one) to analyse the effects of a circadian control (a biologically known physiological control with period 24 hours) on tissue proliferation, in particular tumour growth, with or without therapy. Thus in [33, 34], the authors compare the growth rate (Malthus exponent) of a cell population submitted to different time-periodic controls between them, including the case of a no control (i.e., a control function being replaced by a multiplicative constant set to an average of the control function it is compared to).

In [23], it is proved that when transition rates $K_{i\to i+1}(t,x)$ are time-independent, the stiffer these rates behave as a function of age x, the lower is the Malthus exponent λ. More precisely, if the cycle phase duration probability density function (p.d.f.) $K(x)e^{-\int_0^x K(\xi)\ d\xi}$ (which is indeed a p.d.f., on $\mathbb{R}_+$ provided that $\displaystyle\int_0^{+\infty} K(\xi)\ d\xi = +\infty$) is taken in a family of laws with fixed mean μ and varying variance σ^2, then λ is an increasing function of σ^2. In other words, the higher the incertitude on the phase duration, the higher the growth exponent. This result is not completely original, and it corresponds to the intuitive notion that healthy cell populations are well synchronised with respect to cell cycle timing, passing from one phase to the following one in good order, whereas cancer cells are more loosely coordinated, resulting in a higher growth rate for a cancer cell population.

This being settled, the question of a target for periodic control by physiological or pharmacological inputs may be assessed in the McKendrick model. A rather unexpected result proved in [36] (Theorem 2.1) is that when a time-periodic *gating* control is exerted only on death rates, then the Malthus exponent λ is always higher than its counterpart for an uncontrolled time-stationary model designed with the same time-averaged coefficients. Otherwise said, periodic gating control exerted on death rates enhances proliferation. But if the same periodic control is exerted only on transition rates, then no clear hierarchy can be found between the periodic and the stationary λs [33, 34, 35]. This theoretical finding, combined with the fact that protein p53 is known to exhibit periodic oscillations in case of DNA damage exerted by a cytotoxic drug ([51, 53], see also a recent review and new model for p53 oscillations in [38]), together with the fact that cytotoxic drugs themselves often show variations in their concentrations that are under the dependence of periodically controlled enzymes of the cell metabolism, induces to consider as more likely an action of cytotoxic drugs on cell cycle phase transition rates rather than only directly on death rates.

In [23], an optimisation problem is considered, consisting in minimising the exponential growth rate λ_C of a population of tumour cells submitted to a phase-specific cytotoxic therapy under a toxicity constraint on the population of healthy cells. This constraint is also represented by an exponential growth λ_H to be maintained over a (tunable) constant value Λ. The phase-specific chronotherapy results in the blocking of cells at the G_2/M checkpoint, and subsequent cell death when too much time has been spent in such blocked status, for cells that are committed in the division cycle. As mentioned earlier, in the absence of physiological knowledge on how cell death occurs after cell cycle arrest, subsequent cell death is coarsely represented in numeric simulations in [23] by a maximum number of runs of the division cycle, i.e., a limited number of loops on age x for transition rates. It results after this number is passed in a null transition rate $K_{i-1\to i}(t,a)$ and null boundary term $\displaystyle\int_{\xi\geq 0} K_{i-1\to i}(t,\xi)\ n_{i-1}(t,\xi)\ d\xi$ for all phases i. The model in a 2-phase form has been partly (i.e., without drug control) identified on biological data (an NIH-3T3 cell line, mouse embryonic fibroblasts in culture) by using the FUCCI fluorescence method [74, 75]. Only simulations have been performed, and the model has been only partly identified, but optimal control strategies for a periodic drug delivery are proposed in [23] , that successfully solve the problem, decreasing the cancer growth rate while maintaining the healthy cell population growth rate over a given threshold.

Other works model cytostatic, rather than cytotoxic, effects by an action on the ageing velocity v in Eq. (4). Thus, Hinow *et al.* [47] investigated the effect of lapatinib (a cytostatic drug that is known to become cytotoxic at high doses) on proliferating and non-proliferating cells. To be consistent with experimental data the authors considered a slowing (cytostatic) effect of the drug on the velocity of ageing in the proliferative cell population in G_1 (i.e., with the notations of Eq. (4)), they took $v(a) = 1 - \delta(a,t)$ where the function δ also depended on the drug dose), and simultaneously, at high drug doses, a cytotoxic effect (death term) on the two cell populations.

Another way to represent cell population growth control by cytostatics is to send (and to maintain) proliferating cells in a quiescent phase where they do not proliferate. Gabriel *et al.* [43] investigated the effect of erlotinib, another cytostatic drug, on cancer cells, using an age-structured model that includes a proliferative compartment and a quiescent one. They assumed that the rate of proliferating cells that become quiescent is an increasing function

of the cytostatic drug dose. This simple linear McKendrick model is written as

$$\begin{cases} \dfrac{\partial}{\partial t}p(t,x) + \dfrac{\partial}{\partial x}p(t,x) + \{\mu + K(x)\}\, p(t,x) = 0 \ , \\ p(t,x=0) = 2(1-f)\displaystyle\int_{\xi\geq 0} K(\xi)\, p(t,\xi)\, d\xi \ , \\ p(t,x=0) = p_0(x) \ , \\ \dfrac{d}{dt}Q(t) = 2f\displaystyle\int_{\xi\geq 0} K(\xi)\, p(t,\xi)\, d\xi - \nu Q(t) \ , \\ Q(0) = Q_0 \ , \end{cases} \tag{6}$$

and the drug target here is f, rate of escape at mitosis towards the siding phase Q, f to be enhanced by a cytostatic drug. The model was identified on the human Non Small Cell Lung Cancer (NSCLC) cell line PC-9 submitted to erlotinib.

3.3.2. *Extension to delay differential models.* Following a 30 year-old tradition of models for haematopoiesis that date back to [55], using a distinction between proliferating and nonproliferating (i.e., quiescent) cell compartments, Adimy *et al.* designed a model with continuous age and discrete maturity structure [1]. In its delay-differential version (obtained by integration of an age-structured PDE model along characteristics [42, 72]), the model describes at each maturation stage i the dynamics of both quiescent cells with density x_i and proliferating cells y_i. It may be written as

$$\begin{cases} \dot{x}_i(t) &= -\delta_i x_i(t) - w_i(t) + 2(1-K_i)\displaystyle\int_0^{\tau_i} e^{-\gamma_i a} f_i(a) w_i(t-a)\, da \\ & \qquad\qquad + 2K_{i-1}\displaystyle\int_0^{\tau_{i-1}} e^{-\gamma_{i-1} a} f_{i-1}(a) w_{i-1}(t-a)\, da \ , \\ \dot{y}_i(t) &= -\gamma_i\, y_i(t) + w_i(t) - \displaystyle\int_0^{\tau_i} e^{-\gamma_i a} f_i(a) w_i(t-a)\, da \ , \end{cases} \tag{7}$$

where K_i, with $K_0 = 0$ ($i = 0$ representing the stem cell state), is the rate of cells that differentiate to the next maturation stage $(i+1)$, γ_i and δ_i are death rates at stage i in the proliferating and quiescent states respectively, $w_i(t) := \beta_i(x_i(t))x_i(t)$, where β_i is a nonlinear feedback ("reintroduction function", often taken as a decreasing Hill function with limit zero at infinity, following [55]) from the ith quiescent to the ith proliferating phase. The introduction of the discrete maturity state ($i = 1 \dots I$) allows to represent the action of redifferentiating agents such as ATRA on the differentiation rates K_i, that in AML are zero at some stage i, e.g., at the promyelocyte stage in APL. In this setting, one can also represent the action of cytotoxic drugs by an increase in the death rates γ_i in the proliferating phase, and of cytostatic drugs by a decrease in the feedback functions β_i, considered here as representing (formerly in the boundary terms in the original PDE) the dependence on growth factor receptors that is negatively impacted by cytostatic drugs. Stability analyses were performed and theoretical drug targets, involving both proliferation and differentiation, were proposed on β functions and rates K (see [2, 67, 68] and references therein). They involve an inequality on model parameters at a non trivial equiibrium point, the existence of which is proven under conditions in [67]. Such stability conditions can be guidelines in the future to use such models as a rationale for the delivery of drugs in combined therapies mixing cytotoxic (acting on death rates γ and δ), cytostatic (acting on the feedback function β) and redifferentiating (acting on differentiation rate K) molecules, aiming at re-establishing a lost equilibrium. For the time being, the focus in modelling has been set on combinations between cytotoxics and cytostatics. This is in particular the case

of AML with a mutation of the Flt-3 growth factor receptor (Flt3-ITD gene duplication, resulting in an abnormal tyrosine kinase, that does not need its normal ligand to be activated), which is present in about 30% of all AMLs, generally resulting in poor prognosis [45].

3.3.3. *Other physiologically structured transport equations.* Physiologically structured models have also been used to study the dynamics of metastatic cell population. Instead of considering age of cells in the cell cycle as the main structure variable, these models consider the size of the metastatic colony [11, 21, 48]. Thus, denoting by x the tumour size, Iwata *et al.* [48] assumed that a primary tumour was generated from a single cell at time $t = 0$, grew at rate $v(x)$ and emitted at rate $\beta(x)$ metastatic single cells that developed as the primary tumour. The growth rate $v(x)$ was assumed to follow a Gompertz model:

$$v(x) = \alpha x \log\left(\frac{b}{x}\right) \tag{8}$$

and the evolution of the colony size distribution of metastatic tumours with cell number x at time t was assumed to be governed by a McKendrick model (cf Eq. (4)). So this model is a combination of a Gompertz model and of an age-structured one. In [11] Barbolosi *et al.* proposed a mathematical analysis of this model. Later, Benzekry *et al.* [21] introduced in this model the effect of docetaxel, an M phase-specific cytotoxic drug, using a PK-PD three-compartmental model and an interface model to determine the drug exposure. The effect of this drug was modeled via a death term in the growth velocity. In the same work, they also analysed the effect of several infusion schedules of an anti-angiogenic agent. To do this, they considered an additional equation (ODE) for the time evolution of the carrying capacity, just as done by Hahnfeldt *et al.* in [46] (cf Section 3.2), in which they introduced a death term as a function of the concentration in the anti-angiogenic agent. These authors accounted for the experimentally observed phenomenon of metastatic acceleration after anti-angiogenic therapy (using endostatin) and analysed the influence of several infusion schedules on this phenomenon. Finally, they compared the effect both on the primary tumour and on the number of metastases of several infusion schemes of combination of etoposide (cytotoxic drug) and bevacizumab (anti-angiogenic agent).

Transitions between the phases of the cell cycle are accompanied by changes in DNA content, from 2n to 4n DNA content during S phase, so that models structured by DNA content have also been developed. Basse *et al.* [14] proposed a model for the four phases of the cell cycle in which obviously only cells in S phase undergo DNA changes. To account for DNA variability induced by flow cytometry, the authors also introduced in the equation on the density of cells in S phase with DNA content x at time t a dispersion term. This model enabled them to compare calculated flow cytometry profiles with experimental ones. Later, Basse *et al.* [15, 16] extended this model by adding an apoptosis phase that could be reached via transition from the mitotic phase. The authors also introduced an age structure in the M phase of the cell cycle, so that this phase is in this model They involve structured in both age and DNA content. This extended model enabled them to analyse the effects on tumour cell lines of paclitaxel, an M phase-specific anti-cancer agent known to induce mitotic cell cycle arrest and cell death via a transition from the mitotic phase to the apoptotic one blocks mitotic spindle dissociation, thus preventing cytokinesis, the last part of mitotic phase, during which a dividing cell actually becomes two). The model parameters were determined by fitting them to experimental profiles obtained by cytometry.

Other models consider several physiological variables as structure variables. Thus Bekkal Brikci *et al.* [19, 20] developed an age-structured model that was also structured by the amount of the complex cyclin D/(Cdk4 or 6), known to be the main regulator of the cell cycle at the restriction point R in late G_1 phase, an age after which cells are irreversibly

committed to proceed towards division [60]. The model considers a global proliferative phase that is age- and cyclin D/(Cdk4 or 6)-structured and a quiescent one that is not physiologically structured. The exchanges of cells between the proliferative compartment and the quiescent one depend on Hill functions of the total cell population, as in Mackey's models [55]. Although the inclusion of drug control has been in [20] postponed to 'the future', the model is adapted to represent targets for cytostatics at the level of these exchanges and for cytotoxics either on death rates or on boundary terms for the proliferating population. More recently, Borges *et al.* [25, 26] considered the age-independent version of this model, i.e., a cyclin-structured model, still without drug targets.

3.3.4. *Models integrating space and age-structure.* As mentioned earlier, the most relevant level to describe proliferation and its control by drugs is clearly the cell population level, but the level of local surrounding cell populations must also be considered, in particular to account for the interactions between the tumour and its environment. Bresch *et al.* [27] developed a tumour growth model in which cell cycle regulation also depends on the tumour environment, typically cell density and oxygen level. The authors considered two proliferative phases P_1 and P_2, representing respectively G_1 before the restriction point [60], and the rest of the cell cycle (remainder of G_1 and $S/G_2/M$), two proliferative phases to which a quiescent phase Q is added. They assumed that only proliferative phases were age-structured and they added an advection term to model the passive transport of tumour cells induced by cell division:

$$\begin{cases} \dfrac{\partial P_1}{\partial t} + \dfrac{\partial P_1}{\partial a} + \nabla \cdot (\mathbf{v_{P_1}} P_1) = 0 \ , \\ \dfrac{\partial P_2}{\partial t} + \dfrac{\partial P_2}{\partial a} + \nabla \cdot (\mathbf{v_{P_2}} P_2) = 0 \ , \\ \dfrac{\partial Q}{\partial t} + \nabla \cdot (\mathbf{v_Q} Q) = (1-f) P_1(a = a_{max,P_1}) - \left[\dfrac{\partial f}{\partial t}\right]^+ Q(t^-) \ , \\ P_1(a=0) = 2\ P_2(a = a_{max,P_2}) \ , \\ P_2(a=0) = f P_1(a = a_{max,P_1}) + \left[\dfrac{\partial f}{\partial t}\right]^+ Q(t^-) \ , \end{cases} \tag{9}$$

where a represents the age of cells in each proliferative phase, $\mathbf{v_{P_1}}$, $\mathbf{v_{P_2}}$, $\mathbf{v_Q}$ the velocities in the phases P_1, P_2, Q respectively, a_{max,P_1} and a_{max,P_2} the maximal age a cell can spend in P_1 and P_2 respectively, $[\cdot]^+$ the positive part. The function f is a boolean function that depends on time and space, equal to one if there is no overpopulation and no hypoxia at space location $\mathbf{x}$ and time t, equal to zero else. Assuming that the three velocities were equal and that the total number of tumour and healthy cells was constant gave an additional equation to compute the velocity. Bresch *et al.* [27] analysed the influence on tumour growth of a membrane surrounding this tumour. Ribba *et al.* [73] considered a simplified version of this model as they did not account for the oxygen but they considered the action of matrix metalloproteinases (MMPs). MMPs are enzymes secreted by tumour cells, known to digest the extracellular matrix so as to facilitate local invasion by tumour cells. Using this model, Ribba *et al.* analysed the effect of MMP inhibitors (MMPIs), anti-cancer agents known to reduce cancer growth in animal models but whose clinical development was not as successful as expected (they were too toxic). In this model, MMPIs were assumed to promote the passage of proliferative cells into the quiescent phase at the restriction point. They assessed the therapeutic benefit of MMPIs via a parameter that

compared the proportion of quiescent cells in a population submitted to treatment with the one in the same population without treatment. Later, Billy *et al.* [24], based on the model developed by Bresch *et al.* [27], investigated the effects on tumour growth of an anti-angiogenic therapy. They coupled, via oxygen concentration, the model developed by Bresch *et al.* with a continuous PDE model of angiogenesis that accounts for the density of endothelial cells (ECs, cells that constitute blood vessels), oxygen and some pro- and anti-angiogenic substances. The authors investigated the effect of an anti-VEGF therapy (VEGF being the main pro-angiogenic factor) that consisted in increasing the local concentration of endostatin, an anti-angiogenic factor that competes with VEGF for binding to EC receptors. This therapy was modelled through an endostatin oversecretion since endostatin was known to be endogenously secreted by tumour cells. Thus, in this model, endostatin is assumed to directly target VEGF binding to ECs since an increase of endostatin concentration induces a decrease of the VEGF binding rate to ECs, which leads to lower activation of ECs by VEGF, i.e., lower proliferation and migration rates of ECs and even EC death for high endostatin concentrations (more details can be found in [24] Sections 3 and 4). Such therapy can lead to regression of the vascular network and thus induce hypoxia or even death of tumour cells. Several infusion schedules were studied and their efficacies on the tumour volume were compared. The authors highlighted the existence of a critical local concentration of endostatin below which it was more efficacious on tumour growth to increase the rate of oversecretion of endostatin instead of its duration and above which the opposite was true.

3.4. **Equations for adaptive dynamics models: cell Darwinism.** The idea that cancer is an evolutionary disease is not new, but strangely enough, not many articles on this theme, let alone on mathematical models on Darwinism in cancer cell populations, have been published so far, according to a recent review [3]. The genetic paradigm, i.e., cancer due to a single "renegade" mutated cell developing in a malignant clone, is most often considered as the only explanation of evolution towards cancer, with little attention brought so far to (possibly reversible) environmental effects exerted at the level of cell populations, which may partly explain the present situation. In the perspective of cell Darwinism, which always concerns populations of individual cells, considering drug effects as part of an environmental pressure resulting in selection and possibly speciation (emergence of a *genetically* resistant species) is a rather new idea in mathematical modelling to account for evolution towards drug resistance in a cancer cell population. This relies on equations with a continuous structure variable representing a resistant phenotype ($x = 0$, no resistance; $x = 1$, completely resistant population), which may be reversible (if resistance is due to an epigenetic rather than genetic phenomenon) or not. In models of the type presented below (Eq. (10)), evolution towards acquired drug resistance, i.e., the development of a subpopulation bearing a resistant phenotype, close to $x = 1$, may be the result of mutations, but it may also be the result of exchanges with the environment, without mutations, thus representing in the latter case possibly reversible acquired resistance [54]:

$$\begin{aligned}\frac{\partial}{\partial t}n(x,t) &= \overbrace{\frac{\theta}{1+\alpha c_2(t)}\left(\int r(y)M(y,x)n(y,t)dy - r(x)n(x,t)\right)}^{\text{mutations and renewal}} \\ &\quad + \underbrace{\left(\frac{r(x)}{1+\alpha c_2(t)} - d(x)I(t)\right)n(x,t)}_{\text{growth with cytostatic therapies and death}} - \underbrace{c_1(t)\mu(x)n(x,t).}_{\text{effect of cytotoxic therapies}} \qquad (10)\end{aligned}$$

Here M is a mutation kernel, with radius *a priori* larger in the cancer than in the healthy cell population, θ is the proportion of cells that undergo mutations at mitosis, and, introducing subscripts H and C for healthy and cancer cells n_H and n_C, competition in the environment is represented by variables I_H and I_C that may be only fixed linear combinations of the total healthy and cancer cell populations $\int_{x\geq 0} n_H(x,t)\,dx$ and $\int_{x\geq 0} n_C(x,t)\,dx$, but may also be variables in interaction with the environment, e.g., with cytokines.

3.4.1. *Mutations only.* The main interest of including a drug target on mutation rates is to represent genomic instability in cancer cells by a higher probability of mutation under the influence of a drug. This is presented in the frame of model equation (10) when $\theta \neq 0$. Nevertheless, at least in this setting, mutations do not seem to play the main part in the establishment of a resistant phenotype, yielding only diffusion around a Dirac δ distribution for the dominant phenotype. This rules out the possibility of representing in this model acquired drug resistances only due to mutations of the target, as for instance imatinib resistance, for which mutations of the target, BCR-Abl protein, have been evidenced. Likely, other versions, focusing on mutations, of the same model, should be used in this case.

3.4.2. *Competition for resources and exchanges with the environment.* In this type of model, it is easy to obtain evolution towards resistance without mutations (i.e., setting $\theta = 0$). In fact, the theorems demonstrated in [54] (Theorems 3.1, 3.2, 3.3) state asymptotic convergence towards a single Dirac mass concentrated around a unique value of the phenotypic trait, and these theorems hold with or without mutations. The healthy cell population case is characterised by a homeostatic factor of the form $\dfrac{1}{1+I(t)}$ before the proliferation term $r(x,y)$, where $I(t)$ represents the total (healthy and cancer) cell population, preventing the healthy cell population from exploding, whereas in the cancer population case, no such homeostasis has been put in the evolution equation.The theorems in [54] show that under a cytotoxic therapy, the convergence occurs towards a single Dirac mass (monomorphism of the fittest population) , concentrated around $x = 0$ in the healthy case, and concentrated around a fittest trait $x_C \neq 0$, i.e., a resistant phenotype, in the cancer case.

3.4.3. *Combining cytotoxic and cytostatic effects.* With settings close to those shown in Eq. (10), neglecting mutations, but representing the action of two different drugs *and a 2-dimensional resistance phenotype* (x,y), one corresponding to a cytostatic drug that acts on proliferation, and another one corresponding to a cytotoxic drug that acts on a death term, it is possible to obtain numerically dimorphism of asymptotic traits in the cancer cell population, one fittest subpopulation concentrated around $(1,0)$ and the other around $(0,1)$ (Fig. 2), i.e., asymptotic coexistence of two different subpopulations, one resistant to the cytostatic, the other resistant to the cytotoxic drug. The 2-drug model for tumour cells runs

$$\partial_t n(t,x,y) = \left[\frac{r(x,y)}{1+\mu_2(x,y)c_2(t)} - d(x,y)I(t) - \mu_1(x,y)c_1(t)\right] n(t,x,y), \qquad (11)$$

where c_1 and c_2 represent the effects of a cytotoxic and of a cytostatic drug, respectively, and $I(t)$ is again the total (weighted) population of all cells, healthy and tumour, the term $d(x,y)$ thus representing competition for space and nutrients, while μ_1 and μ_2 represent the targets for cytotoxic and cytostatic drugs, respectively.

Simulation results, with particular choices for the target functions (not shown), taking into account the fact that developing resistance hinders proliferation capacities, and with initial conditions centered around mean values $(x,y) = (0.5, 0.5)$ show the possibility

of evolution towards a dimorphic cell population in cancer cells, whereas the healthy cell population, with a homeostatic factor multiplying its proliferation term (see above), on the contrary evolves towards total sensitivity, as illustrated on Fig. 1 and 2.

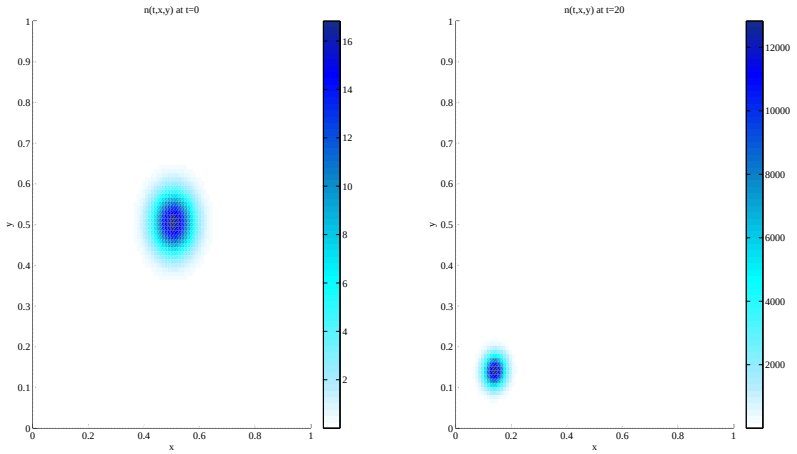

FIGURE 1. Healthy cells. Starting (t=0, left) from an average 2d phenotype [$(x, y) = (0.5, 0.5)$], evolution towards total sensitivity (t=80, right): no resistance. Model, simulation and figure by Tommaso Lorenzi.

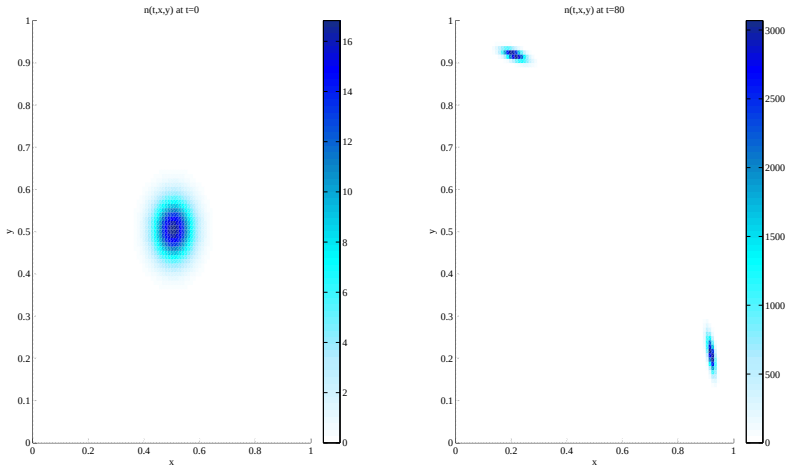

FIGURE 2. Cancer cells. Starting (t=0, left) from the same average 2d phenotype [$(x, y) = (0.5, 0.5)$], evolution towards two separate resistant clones (t=80, right), one resistant to the cytotoxic drug, the other one to the cytostatic drug. Model, simulation and figure by Tommaso Lorenzi.

It is also possible, as numerically shown in [54], Fig. 6.6, to obtain different asymptotic behaviours, in particular evolution towards resistance or extinction of the cancer cell population while keeping healthy cells alive, only by varying constant doses of the two drugs. This may be considered as a step towards drug delivery optimisation with respect to the question of avoiding drug resistance, by combining cytotoxic and cytostatic drugs.

Note that one can also (work underway) represent simultaneously space and an evolutionary phenotype in PDE or integro-differential models accounting for the evolution of tumour spheroids submitted to an externally delivered therapy. In this case, a 1d radial spatial variable is a relevant structure variable that must be considered together with the cell phenotype responsible for drug resistance.

4. **Conclusion.** We have reviewed in this article some old and more recent models of proliferating cell population dynamics designed to theoretically solve problems of therapeutic optimisation encountered in the clinic of cancers, always considering them from the point of view of drug target representation. Polychemotherapy is usually the rule in oncology - with a few known exceptions such as imatinib in chronic myelogenous leukaemia -, so that designing a rationale to optimally combine treatments acting on different functional targets in the physiological mechanisms that control proliferation in cell populations should eventually be a help in the clinic. This involves taking into account in multiscale mathematical models the moving physiological knowledge of these mechanisms, of how old and new drugs can modify them, and of how they can be investigated at the different levels of observation: single cell, cell population, and whole body as a collection of interacting cell populations. We stress that this program implies frequent interactions, going far beyond an attitude of sort of 'scientific service providers', between teams of mathematicians, biologists and clinicians, with mutual efforts to understand how each discipline can benefit of each others' representations and findings. We hope that this review of models and results, seen from the point of view of drug targets, can be helpful to this aim.

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