Available online at www.sciencedirect.com

SciVerse ScienceDirect

Mathematics and Computers in Simulation 96 (2014) 66–94

MATHEMATICS AND COMPUTERS IN SIMULATION

www.elsevier.com/locate/matcom

Original article

Synchronisation and control of proliferation in cycling cell population models with age structure

Frédérique Billy [a,b], Jean Clairambault [a,b,*], Olivier Fercoq [c,d], Stéphane Gaubert [c,d], Thomas Lepoutre [e,f], Thomas Ouillon [g], Shoko Saito [h,1]

[a] *Inria Paris-Rocquencourt, Domaine de Voluceau, Rocquencourt, B.P. 105, F-78153, Le Chesnay, France*
[b] *UPMC Univ Paris 06, UMR 7598, Laboratoire Jacques-Louis Lions, F-75005, Paris, France*
[c] *Inria Saclay Ile-de-France, Parc Orsay Université, 4 rue Jacques Monod, F-91893, Orsay Cedex, France*
[d] *Centre de Mathématiques Appliquées, CNRS UMR 7641, École Polytechnique, Route de Saclay, F-91128, Palaiseau Cedex, France*
[e] *Inria Grenoble - Rhône-Alpes, Inovallée, 655 avenue de l'Europe, Montbonnot, F-38 334, Saint Ismier Cedex, France*
[f] *Université de Lyon, F-69000, Lyon, France; Université Lyon 1, CNRS UMR 5208, Institut Camille Jordan, 43 Bd du 11 Novembre 1918, F-69622, Villeurbanne Cedex, France*
[g] *ENSTA ParisTech, 32 Bd Victor, F-75739, Paris Cedex 15, France*
[h] *Department of Genetics, Center for Biomedical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands*

Received 18 July 2011; received in revised form 21 December 2011; accepted 22 March 2012
Available online 4 April 2012

Abstract

We present and analyse in this article a mathematical question with a biological origin, the theoretical treatment of which may have far-reaching implications in the practical treatment of cancers.

Starting from biological and clinical observations on cancer cells, tumour-bearing laboratory rodents, and patients with cancer, we ask from a theoretical biology viewpoint questions that may be transcribed, using physiologically based modelling of cell proliferation dynamics, into mathematical questions.

We then show how recent fluorescence-based image modelling techniques performed at the single cell level in proliferating cell populations allow to identify model parameters and how this may be applied to investigate healthy and cancer cell populations.

Finally, we show how this modelling approach allows us to design original optimisation methods for anticancer therapeutics, in particular chronotherapeutics, by controlling eigenvalues of the differential operators underlying the cell proliferation dynamics, in tumour and in healthy cell populations. We propose a numerical algorithm to implement these principles.
© 2012 IMACS. Published by Elsevier B.V. All rights reserved.

Keywords: Mathematical models; Cell population dynamics; Age-structured models; Cell division cycle; Drug delivery optimisation

1. Experimental and theoretical motivations

Tissue proliferation in living organisms always relies on the cell division cycle: one cell becomes two after a sequence of molecular events that is physiologically controlled at each step of the cycle at so-called checkpoints [63,71]. This

* Corresponding author.
E-mail addresses: jean.clairambault@inria.fr (J. Clairambault), olivier.fercoq@inria.fr (O. Fercoq), stephane.gaubert@inria.fr (S. Gaubert), thomas.lepoutre@inria.fr (T. Lepoutre), thomas.ouillon@gmail.com (T. Ouillon), ssaito@md.tsukuba.ac.jp (S. Saito).
[1] Current address: Department of Infection Biology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.

0378-4754/$36.00 © 2012 IMACS. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.matcom.2012.03.005

process occurs in all renewing tissues, healthy or tumour, but in tumour tissues part of these control mechanisms are inefficient, resulting in uncontrolled tissue growth which may be given as a definition of cancer.

At the initial local stages of cancer (*i.e.*, still without more invasive processes involving tumour neoangiogenesis, digestion of the extracellular matrix and metastases), deficiencies in the control of cell cycle checkpoints, *e.g.*, involving mutated protein p53, are the main factors responsible for this disrupted control of tissue growth.

The representation of the dynamics of the division cycle in proliferating cell proliferations by physiologically structured partial differential equations (PDEs), which dates back to McKendrick [67], is a natural frame to model proliferation in cell populations, healthy or tumour. Furthermore, the inclusion in such models of targets for its physiological and pharmacological control allows to develop mathematical methods of their analysis and control [28].

1.1. Circadian clocks and tumour growth

In the physiological control of the cell division cycle, the role of molecular circadian clocks, which exist in all nucleated cells and are themselves under the control of a central hypothalamic neuronal clock, has been evidenced by numerous animal experiments and is also supported by various clinical observations. These clocks, in the constitution of which about 15 genes have been shown to take part, exert a rhythmic regulating control with a period of approximately 24 h (hence their name: *circa diem* = about one day) on hormonal, metabolic, behavioural and proliferative processes [78,82]. The first of these genes to be discovered were the Per gene in the fruit fly *Drosophila Melanogaster* by Konopka and Benzer in 1971 [53], and in mammals, the Clock gene by Takahashi in 1994 [88]. Their disruption may impair all these physiological processes in an extended manner. It has been experimentally shown by transgenesis experiments that Per2 knock-out transgenic mice are more prone to develop radiation-induced cancers than wild type mice [41].

Similarly, in experiments performed by a totally different team, it has been shown that tumour-bearing mice submitted to artificial strong perturbations of their circadian rhythms constantly exhibit accelerated tumour growth. In a series of articles reporting these experimental observations on two groups of tumour-bearing laboratory rodents [39,40] (the tumour was a fast growing murine tumour positioned in a subcutaneous, easily accessible, site), one with a disrupted central circadian clock, the other with a physiologically light-entrained clock as a control group, this has been demonstrated by comparing tumour growth curves. These observations were confirmed and supported by measurements of clock gene expression by quantitative real time polymerase chain reaction (qRTPCR). Furthermore, it was shown that in the disrupted clock group, a partial correction of this tumour growth enhancement was obtained by re-entraining circadian clocks by controlled restricted feeding at fixed and unusual times for rodents (during daylight) [39], thus opening the way to the idea that it could be possible to add an external control to reinforce these physiologically controlled checkpoints when they are deficient.

It has also been observed in clinical settings that patients with cancer, whose circadian rhythms (rest/activity, blood cortisol) were damped or ablated, showed clinically more fatigue and had poorer life prognosis. They also had higher blood levels of cytokines [79], which are emitted by tumour cells, or by immune cells that surround tumours; at least one of these cytokines, TGF_α, has been experimentally shown, when directly infused in the cerebrospinal fluid of mice (into the third ventricle), to severely disrupt their circadian rhythms, as evidenced on rest-activity and sleep-wake cycles [54].

Whether or not circadian clocks play an essential role in controlling checkpoints of the cell division cycle remains to be more documented, both experimentally, by performing measurements in cell cultures and in living whole organisms, and theoretically, by using and analysing combined mathematical models of molecular circadian clocks and of the cell division cycle in cell populations [28,31–33,35,36]. Nevertheless, we will develop here the concept of *synchronisation* between phases of the division cycle in a proliferating cell population, to show that the less synchronised phases are within a cell population (*i.e.*, the looser are cell cycle phase transitions), the faster is proliferation measured by a Malthus-like growth exponent, first eigenvalue of the theoretical tissue growth process.

Furthermore, since circadian clock proteins such as Bmal1 and Per2 have been shown to control cyclin dependent kinases which themselves control in particular G_1/S and G_2/M phase transitions [65], it is not unlikely from a theoretical biology point of view that circadian clocks control cell cycle phase synchronisation, and by this way, proliferation of the cell population. Consistent with this speculation and the above mentioned experiments on cancer growth enhancement by circadian clock disruption is the fact that in patients with cancer, the less expressed are physiological circadian rhythms, *e.g.*, of rest-activity or blood cortisol, the poorer is the prognosis and the response to cancer treatments [72].

Download English Version:

https://daneshyari.com/en/article/1139340

Download Persian Version:

https://daneshyari.com/article/1139340

Daneshyari.com