MathSys miniproject: Robustness and design of optimal cancer chronotherapies. Supervisor: Burroughs (Mathematics). Second supervisor: Annabelle Ballesta (Institute Curie, Paris)

Outline and context.

Chronotherapy is the arm of cancer therapy that exploits the fact that cancer mutations often disrupt the cell's circadian rhythm [1], i.e. synchronisation of cellular function with the 24 hour clock cycle that governs activity in all healthy cells and synchronises body activity to the day/night cycle. In particular, healthy cells typically divide during the night, whilst cancer cells, in contrast, have a deteriorated circadian clock and thus lose this synchronisation with the body to divide at night. Synchronisation further deteriorates as the cancer becomes more advanced. This project will examine optimisation of drug therapies that target cell division, specifically the concentration of the drug can be modulated by an infusion device during the circadian cycle thereby reducing toxicity to normal cells whilst remaining effective against cancer cells. You will use ordinary differential equation (ODE) models of tumour growth with the circadian clock implemented by a time dependent division rate. To determine optimal therapy design, you will use Pontryagin's maximum principle, (PMP), developed in the 1940s and since developed into an extremely powerful tool. The function to be optimised will include a periodic toxicity cost (to normal cells). You will use PMP for non-autonomous systems (systems with explicit time dependence).

Techniques and models.

The simplest set up takes the form of a tumour growth model with growth totally decoupled from the bodies circadian clock,

$$\frac{dN(t)}{dt} = (f(N(t)) - du(t))N(t),\ N(0) = N_0 \text{ (detection threshold)}$$

where $N(t)$ is the tumour size at time t, $f(N) \geq 0$ is the cell doubling rate, eg for logistic growth $f(N) = \lambda(1-N/K)$, and $u(t)$ is the drug concentration at time t, normalised such that the maximum tolerated dose $= 1$, *i.e.* $0 \leq u \leq 1$. The cost function to be minimised incorporates a cost for tumour size at the end of treatment (time T) and a running toxicity cost to normal cells,

$$J[x, u, t] = rN(T) + \int_0^T (1 - \alpha\cos(2\pi t))u(t)dt$$

where $\alpha < 1$ is a positive constant that callibrates toxicity to normal cells throughout the day. Time is measured in days.

More realistic models would incorporate a cell division model with the drug targeting the cells in the process of division, a circadian division rate for partial clock disruption, eg $\lambda(t) = \lambda_0(1 + \beta\cos(2\pi t))$, and a drug clearance kinetics. Drug pharmacokinetic models can also be used. The optimal control $u(t)$ is then determined from PMP, potentially analytically for simpler models, and numerically otherwise. In brief, you construct the Hamiltonian incorporating the constraints $H = r + pf$, costate variable $p(t)$ and minimise/maximise H at each time point to find $u(t)$.

Required skills. An understanding of ODEs, eg solutions methods including phase planes. An interest in computation is useful, and experience with a high level language such as MatLab, python or C++ may be required.

Key questions and deliverables.

Key things to address will be (time permitting, probably at most 3):

1. Optimal controls under various cell division models (1-3 compartments), various cost functions and drug clearance.

2. Optimal controls under full versus partial decoupling of cancer cell division from the circadian rhythm.

3. The effect of cancer heterogeneity (cancer cells of both full and partial rhythm loss).

4. Maintenance controls where cure is impossible because of resistant clones. The aim is to maximise patient lifetime [2].

5. The effect of variability in the bodies circadian rhythm – the strength and coherence of the clock in normal cells. Women and men in fact differ in the strengths and phases of their clocks, whilst shift workers have poor circadian rhythms, which is itself a risk factor of cancer. Here you would examine how the optimal therapy can be made robust to such effects.

Relations to the real-world.

Cancer is one of the leading killers today, with about 1/3 of people in the UK getting cancer within their lifetime, with some cancers still incurable. Cancer is a heterogeneous disease, with cancers of different tissues having different prognosis, treatment and models. This project addresses an emerging therapy, modern technology making timed infusion both practical and effective.

Possibilities for a PhD.

This project naturally leads into a number of PhD projects depending on interests. Possibilities include, but not limited to,

1. Cancer modelling and optimisation. For instance working with chronotherapy experts in Paris at the Institut Curie, one of the leading Cancer Centre in France. There is also an emerging field looking at optimal game theory approaches in cancer therapy that has seen substantial success recently in personalised therapy.

2. Optimal control approaches in biology systems. This PhD would examine optimisation problems in stochastic biological systems using the dynamic programming formulation of optimisation (the Hamilton-Jacobi-Bellman equations) that is highly flexible and can be used for optimal control analysis of stochastic differential equations for example. Possible biological problems include cancer therapy (stochastic models, with collaborators in WMS and/or Paris), (human) cell division (with collaborators in WMS, Netherlands) and epidemics (with collaborators in SBIDER).

References

[1] Annabelle Ballesta, Pasquale F. Innominato, Robert Dallmann, David A. Rand, and Francis A. Lévi. Systems chronotherapeutics. *Pharmacological Reviews*, 69(2):161–199, 2017.

[2] James M Greene, Cynthia Sanchez-Tapia, and Eduardo D Sontag. Mathematical Details on a Cancer Resistance Model. *Frontiers in bioengineering and biotechnology*, 8:501–501, June 2020.