Modelling Tumour-Nerve Interactions

Biological Background

It has been empirically known for long time that a connection existed between tumour progression and the nervous system. The first properly scientific explanation of this phenomenon could be formulated after the discovery of the first neurotransmitter in 1915. The connections between cancer development and nerves are bilateral and are referred to as the *neuro-neoplastic synapse*:

- **Indirect Effects** (perineural invasion, immunosuppression...)
- **Direct Effects** (neurotransmitters induce proliferation, survival and migration of tumour cells)

The term *neoneurogenesis* denotes the process by which “tumors initiate their own innervation by the release of neurotrophic factors in analogy to lymphangiogenesis and neoangiogenesis”[1].

Questions:

- Why do tumour cell disaggregate?
- Neurotransmitters can alter cancer cell shape and attachment to other cells and to the ECM
- What induces cancer cells to extravasate and colonise a new tissue?  
  - “Seed and soil” hypothesis (Paget, 1889)
  - Tumour cells follow blood and lymphatic routes (Ewing, 1928)
  - The success of the metastatic cells depends on their ability to adapt to the new “soil” (Fidler, 2003)

Distinction between *sympathetic* and *parasympathetic* nerves

*...and increasing $s$ (stress).*

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Mathematical Model

We focus on prostate cancer and we consider the following variables:

- $T_p$: Primary tumour cells (cells/mm$^3$)
- $T_m$: Migrating tumour cells (cells/mm$^3$)
- $G$: Nerve Growth Factor (pg/mm$^3$)
- $A$: Axon Guidance Molecules (pg/mm$^3$)
- $S$: Sympathetic nerve cells (cells/mm$^3$)
- $P$: Parasympathetic nerve cells (cells/mm$^3$)
- $N_a$: Norepinephrine (pg/mm$^3$)
- $N_s$: Acetylcholine (pg/mm$^3$)

(*$T_m$ is the only quantity “outside” the main domain). The interactions among the variables are described by the following equations:

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\begin{align*}
\frac{dT_p}{dt} &= \frac{7}{8} \left( r_T + \frac{G}{\tau_1 + \tau_2 G} \right) \left( 1 - \frac{T_p}{k_T} \right) \left( \frac{T_p}{\theta(N_n)} - 1 \right) T_p - d_T (1 + \delta A) T_p - (\mu_0 + \mu_1 A + \mu_2 N_a) T_p \\
\frac{dT_m}{dt} &= \left( r_{Tm} - d_T \right) T_m + (\mu_0 + \mu_1 A + \mu_2 N_a) T_p \\
\frac{dG}{dt} &= s_G T_p d_G - [\gamma_1 T_p + \gamma_2 (S + P)] G \\
\frac{dA}{dt} &= s_A T_p d_A - [\gamma_3 T_p + \gamma_4 (S + P)] A \\
\frac{dS}{dt} &= r_S \left( 1 - \frac{S}{k_S} \right) S + \left( \frac{G}{\alpha_1 + \alpha_2 G} + \frac{A}{\alpha_3 + \alpha_4 A} \right) S \\
\frac{dP}{dt} &= r_P \left( 1 - \frac{P}{k_P} \right) P + \left( \frac{G}{\pi_1 + \pi_2 G} + \frac{A}{\pi_3 + \pi_4 A} \right) P \\
\frac{dN_a}{dt} &= c_a + s_s S - d_n N_n - \gamma_5 T_p N_n \\
\frac{dN_s}{dt} &= c_a + s_s P - d_n N_n - \gamma_6 T_p N_a \\
\end{align*}
\]

where: $\theta(N_n) = \frac{\theta_1}{1 + \theta_2 N_n}$
and most of the parameters and initial conditions have been estimated from real datasets.

SIMULATIONS: