A Model Describing the Effect of P-gp Pumps on Drug Resistance in Solid Tumors

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Outline

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Resistance to chemotherapy remains (one of) the largest obstacle for cancer treatment.

The two main mechanisms for resistance are selection and induction.

The over-expression of P-glycoprotein (P-gp) pumps is widely understood to play a large role in multi-drug resistance (MDR).
Drug Resistance

Housman et. al (2014)
Heterogeneity

- Resistance is considered based on the amount of P-gp pumps on any given cell.

- The current model breaks this into a discrete case in which a cell is either "sensitive" or "resistant" to therapy.

- Sensitive cells can become temporarily resistant due to proximity to resistant cells. Intracellular membrane nanotubes act as short distance P-gp carriers.
Duran et. al (2016) created a simple ODE model to describe transfer of drug resistance with P-gp pumps.

\[
\begin{align*}
\frac{dS}{dt} &= \frac{S}{\tau_S} \left(1 - \frac{R+S+S_R}{K}\right) - \frac{SR}{\tau_c} + \frac{S_R}{\tau_*} \\
\frac{dR}{dt} &= \frac{R}{\tau_r} \left(1 - \frac{R+S+S_R}{K}\right) \\
\frac{dS_R}{dt} &= \frac{S_R}{\tau_r} \left(1 - \frac{R+S+S_R}{K}\right) + \frac{SR}{\tau_c} - \frac{S_R}{\tau_*}
\end{align*}
\]
Greene et. al (2014)
Integro-Differential Equation Model

\[ \begin{align*}
\frac{dS_q}{dt} &= -\alpha_{sp} S_q(t) - \alpha_{asq} S_q(t) + 2 \int_0^t f_p(t - t_*; \mu, \sigma)(1 - \xi) \alpha_{sp} S_q(t_*)(1 - \int_{t_*}^t \alpha_{asp}(s) \, ds) \, dt_* \\
&\quad + 2 \int_0^t f_p(t - t_*; \mu, \sigma) \xi \alpha_{sp} S_q(t_*)(1 - \int_{t_*}^t \alpha_{asp}(s) \, ds) \, dt_*, \\
\frac{dR_q}{dt} &= -\alpha_{rp} R_q(t) - \alpha_{arq} R_q(t) + 2 \int_0^t f_p(t - t_*; \mu, \sigma) \alpha_{rp} R_q(t_*)(1 - \int_{t_*}^t \alpha_{arp}(s) \, ds) \, dt_*, \\
\frac{dS_p}{dt} &= (1 - \xi) \alpha_{sp} S_q(t) - \alpha_{asp} S_p - \int_0^t f_p(t - t_*; \mu, \sigma)(1 - \xi) \alpha_{sp} S_q(t_*)(1 - \int_{t_*}^t \alpha_{asp}(s) \, ds) \, dt_* \\
\frac{dR_p}{dt} &= \alpha_{rp} R_q(t) - \alpha_{arp} R_p - \int_0^t f_p(t - t_*; \mu, \sigma) \alpha_{rp} R_q(t_*)(1 - \int_{t_*}^t \alpha_{arp}(s) \, ds) \, dt_* \\
\frac{dT_p}{dt} &= \xi \alpha_{sp} S_q - \alpha_{atp} T_p - \int_0^t f_p(t - t_*; \mu, \sigma) \xi \alpha_{sp} S_q(t_*)(1 - \int_{t_*}^t \alpha_{asp}(s) \, ds) \, dt_* \\
\frac{dA}{dt} &= \alpha_{asq} S_q + \alpha_{arq} R_q + \alpha_{asp} S_p + \alpha_{arp} R_p + \alpha_{atp} T_p \\
&\quad - \int_0^t f_a(t - t_*)[\alpha_{asq} S_q(t_*) + \alpha_{arq} R_q(t_*) + \alpha_{asp} S_p(t_*) + \alpha_{arp} R_p(t_*) + \alpha_{atp} T_p(t_*)] \, dt_*,
\end{align*} \]
Comparison

Duran et. al. (2016)
Comparison

Duran et. al. (2016)

Percentage of Sensitive Cells

Percentage of Resistant Cells
Comparison

Duran et al. (2016)
Results

The initial jump in resistant population is the result of the transition from Sq to Tp.
Results

Overall Population

Time
Population

$2 \times 10^5$
Immediate Steps

- We’ll amend the model to allow for temporary resistance to last more than one generation.
- Once we’re satisfied with this work we’ll add a cytotoxic drug term.

Future Step

- Eventually we’ll change resistance from discrete to continuous to turn this into a PDE model.