

# CHIMERA: Chemotherapy - Surgery Sequencing Infusion

## Notes:

Patient-adaptive Automated Sequencing of chemotherapeutic and surgical treatments (Combining Mechanistic & Learning Models)

## Topics:

- \* Cancer growth,
- \* effects of chemo & op
- \* cell-kill hypotheses
- \* phenotypic states switching
- \* Sequencing treatments (neoadjuvant vs. adjuvant)
- \* models of chemotherapy

## Context:

- Breast cancer sequencing chemo-surgery (adjuvant vs. neoadjuvant)
- Why adjuvant & neoadjuvant?
- No difference on average patients, but what is the best course of action for a particular patient? → Personalized medicine
- Quantifiable patient specific factors to determine the sequencing.
  - Patient specific factors are tumor growth & treatment parameters

①

## Model building

\* Model for personalized sequencing should include tumor cell growth & the effects of chemo & surgery under cell-kill hypotheses.

Sequence, tumor size  $t_0$  is  $M_0$  diagnosed

### 1. Adjuvant chemo

At  $t_0 > 0$  surgery removes a fraction of tumor cells and subsequently chemo with predetermined killing rate  $1 - e^{-k_s t}$

Fuel size  $M_{sc}$  at  $t > 0$

### 2. Neo-adjuvant chemo

At  $t > 0$  chemo is administered with a predefined killing rate  $1 - e^{-k_f t}$   
Surgery removes  $1 - e^{-k_s t}$  cells  
and the fuel size is  $N_{sc}$

The question is  $N_{sc} > N_{cs}$ ?

Let  $P(t, N)$  be the pharmacodynamic & pharmacokinetic effects of disease and  $f(N)$  the tumor growth model

for sequence 1 (adjuvant disease)

$$\left\{ \begin{array}{l} \text{before surgery} \\ \text{after surgery} \end{array} \right. \left\{ \begin{array}{l} \frac{dn_1}{dt} = f(n_1), n_1(0) = N_0, t \in [0, t_0] \\ \frac{dN_1}{dt} = f(n_1) - P(t, n_1) \\ N_1(t_0) = e^{-k_s} \cdot n_1(t_0) \\ t \in [t_0, t_f] \end{array} \right.$$

$(N_{sc} = N_1(t_f))$

for sequence 2 (neoadjuvant disease)

$$\left\{ \begin{array}{l} \text{before disease onset} \\ \text{after disease onset} \end{array} \right. \left\{ \begin{array}{l} \frac{dn_2}{dt} = f(n_2), n_2(0) = N_0, t \in [0, t_0] \\ \frac{dN_2}{dt} = f(n_2) - P(t, n_2), N_2(t_0) = n_2(t_0) \\ (3) \\ t \in [t_0, t_f] \end{array} \right.$$

$$N_{CS} = e^{-k_s \cdot N_2 (+f)}$$

## Cell-kill hypotheses

Log-Kill hypothesis:  $P(t, N) = c(t) \cdot N$

Norton-Simon hypothesis:  $P(t, N) = c(t) \cdot f(N)$

$c(t)$  function proportional to drug concentration at time  $t$   
 and  $f(N)$  is model of tumor growth

Under log kill hypothesis  $N_{CS} < N_{SC}$   
 (Kobayashi et al.)

Under Norton-Simon hypothesis

$$N_{CS} < N_{SC}$$

$$N_{CS} > N_{SC}$$

Norton Simon  $\rightarrow$  kinetic resistance of tumors. led to the notion of dose density in tumor scheduling

- Pharmacokinetics & pharmacodynamics describe the distribution of chemotherapeutics in the body and their effects.

Objectives:

- \* Learn growth model from data of multiple cell-lines of Breast cancer to fit in the Squeaky Scheme
- \* Learn pharmacodynamics & pharmacokinetics ( $P(t, N)$ ) for dose response & optimize drug regimes to overcome tumor kinetic resistance.

Close Taxane (Paclitaxel) uptake as  $P(t, N)$  in the sequencing equation. (Kuh et al.)<sup>2000</sup>)

---

\* Describe Paclitaxel behavior

\* from Hunter-Simon hypothesis

$$P(t, N) = c(t)f(N)$$

where  $c(t)$  function proportional to drug concentration

$f(N)$  growth model (e.g. Gompertz)

$$\textcircled{*} \quad \left\{ \begin{array}{l} \frac{dG_{T,C}}{dt} = (C_{T,m} - C_{T,C}) \frac{CL_f}{V_0} - k_N G_{T,C} \\ \frac{dG_{T,m}}{dt} = (C_{T,C} - C_{T,m}) CL_f \cdot N \cdot e^{k_N t} \end{array} \right.$$

$C_{T,m}$  - free drug medium

$C_{T,C}$  - free drug cell

$C_{T,m}$  - total concentration medium

$C_{T,C}$  - total conc. in cell

$V_0$  - vol. single cell

$V_m$

$CL_f$  - clearance (diffusion)

For each patient we build a model to predict the sequencing based on temporal evolution (ODE) when we know the tumor growth ( $f(N)$ ) and the plasma co-dynamics & pharmacokinetics (drug transport, binding) ( $PG(N)$ ) for personalized prediction.

### Pharmacokinetics of Paclitaxel

- Intracellular concentration of paclitaxel is critical.
- Challenge in finding optimal treatment schedule due to minimal understanding of paclitaxel

### Plasma co-dynamics

= drug effect as function of drug concentration and treatment duration

- cell volume of MCF7 cells using imaging : (microscopy :  $164 \times 200 \mu\text{m}^2$ )

$$V = \frac{\pi}{6} L W^2 \quad \begin{array}{l} L - \text{max cell diameter} \\ W - \text{min cell diameter} \end{array}$$

Pharmacokinetics of uptake, binding & efflux from tumor cells.

Kuh et al. Table 1. Paclitaxel accumulation in cells

- A. Initial Cell Density
- B. Cell density at 24h
- C. Initial  $C_{total, m}$
- D.  $C_{total, m}$  at 24h

Fig 1 eq.

~~\* pg 6~~

~~Fig. 2~~

Drug uptake as fn.  
of cell density & drug in culture

Fig 3. intracellular concentration  
of Paclitaxel in Time (left)

Time dependent changes in total cell volume at different intracellular drug concentrations of Paclitaxel

$$V_c = V_{one\ cell} \cdot \text{cell number}$$

$$V_c = V_{one\ cell} \cdot ICH \cdot e^{K_{cell\ number} t}$$

$$V_{one\ cell} = \frac{\text{avg cell volume}}{ICH} = \frac{\text{initial cell volume}}{\text{initial cell number}}$$

$K_{cell\ number}$  = rate constant for changes in cell number due to Paclitaxel

(8)