The Evolution and Ecology of AT Models: a partial survey

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Outline and vocabulary

- Early models
- Current ecology of Adaptive Therapy modeling
- Future directions

Focus on containment treatments.

◇ Continuous AT / containment : stabilizes tumor at a certain size

◇ Intermittent AT : stabilizes between two thresholds, on-off treatment

◇ Maximal Tolerated Dose (MTD)

Simple models : sensitive and resistant tumor cells + single drug.

(N.B : throughout, the notation differs from original articles)

R. Martin, K.L. Teo, R. Minchin & M. Fischer (1992)

2 types of tumor cells : S sensitive, R fully resistant, $N = S + R$

$$\dot{R} = g(N)(R + \mu S), \quad \text{with } g(N) \text{ decreasing, } \mu \text{ mutation}$$

Goal : Maximize survival time (time at which $N > N_{crit}$)

Assumption : $S(t)$ perfectly tunable, chosen to minimize $\dot{R}(t)$

Trade-off : S large maximimizes competition, but also mutations.

- $R < \overline{R} \rightarrow S$ small (minimize mutations) *
- $R > \overline{R} \rightarrow S$ large (maximize competition) *

* This is what is intuitively expected, and what Hansen et al. (2017) show in specific cases, but not true for all functions $g(N)$.

3 special cases

1. Exponential growth : $g(N) = \rho \rightarrow$ MTD slightly better
2. Logistic : $g(N) = \rho(1 - N/K) \rightarrow$ MTD and containment comparable
3. Gompertz : $g(N) = \rho \ln(K/N) \rightarrow$ containment much better.

Hansen et al. (2017) : pedagogical treatment of (mostly) logistic case

+ add various types of resistance costs + resistance costs not needed.

V. & Noble (2020) : impact of ongoing mutations may be quantified, very small effect on survival time.

H. Monro and E. Gaffney (2009)

Simulations of Gompertzian model with Norton-Simon kill-rate :

$$\begin{array}{lrcl} \text{sensitive} & \dot{S} & = & \rho \ln(K/N)(1-\lambda C-\mu)S \\ \text{resistant} & \dot{R} & = & \rho \ln(K/N)(R+\mu S) \end{array}$$

with K carrying capacity, λ sensitivity, C dose, μ mutation.

Questions : best constant dose ? best treatment starting time ?

Results : moderate dose + delaying treatment increases survival time.

- very high dose $\rightarrow$ death from resistant cells
- very low dose $\rightarrow$ death from sensitive cells

$\hookrightarrow$ Optimal dose strikes a balance.

Moreover, delaying treatment increases competition.

Gatenby et al. (2009) : Adaptive Therapy

Coined the word + different spirit + first paper with preclinical data

A mysterious model + first frequency-dependent model, similar to :

$$\dot{N}_i/N_i \quad = \quad \rho \frac{w_i}{\overline{w}} - \lambda_i \, C \, e$$

- N_i : number of cells of type i
- $\overline{w} = \sum_i \frac{N_i}{N} w_i$ average fitness parameter ;
- $e(t)$ environmental sensitivity (dynamics unshown)

Simulations with 5 types : fittest but most sensitive, less fit & sensitive, less fit & resistant, environmentally resistant, fittest & resistant.

$\hookrightarrow$ AT improves on MTD (unless fittest & resistant type dominant)

Silva et al. (2012)

Discrete-time, frequency dependent model similar to :

$$\begin{aligned} \dot{S}/S &= \rho_s(\textit{other treatment})\frac{S}{S+R} - \lambda_s C \simeq \rho_s - \lambda_s C \quad \text{if } R << S \\ \dot{R}/R &= \rho_r(\textit{other treatment})\frac{R}{S+R} - \lambda_r C \simeq -\lambda_r C \quad \text{if } R << S \end{aligned}$$

λ_s, λ_r sensitivity to treatment ; ρ_s, ρ_r affected by auxiliary treatment

$\hookrightarrow$ resistance cost may be increased to improve AT.

Issue : basic model too favorable to AT.

Bacevic & Noble et al. (2017) : replace $\frac{R}{S+R}$ by $f(R)$ with $f(0) > 0$.

$\hookrightarrow$ key-parameter is $f(0)$: relative fitness of resistant cells when rare.

Zhang et al. (2017), Cunningham et al. (2018)

Three types Lotka-Volterra model : 2 sensitive + 1 fully resistant

$$\frac{\dot{N}_i}{N_i} = \rho_i \left(1 - \frac{\sum_{j=1}^{3} \alpha_{ij} N_j}{K_i(treatment)}\right)$$

N_i : cells of type i, K_i carrying capacity, α_{ij} competition-coefficient.

Whether there is a cost of resistance is debatable (I would say no)

Compare Intermittent AT to MTD and metronomic via simulations.

Famous as in paper reporting results of first clinical trial

But other models would have generated similar motivation

Moreover, somewhat complex and imprecise, and led to confusions.

Other Lotka-Volterra models

Carrère (2017) :

$$\begin{aligned} \dot{S}/S &= \rho\left(1-\frac{R+S}{K}\right)-\lambda C \\ \dot{R}/R &= \rho\left(1-\frac{R+\alpha S}{K}\right), \quad \alpha>1 \end{aligned}$$

Standard treatment impact, α potentially large (cost of resistance + indefinite containment), and not simulations but optimal control.

Carrère and Zidani (2020) : uncertainty on parameters + staying below a maximal acceptable tumor size.

Pouchol et al (2018) : infinite number of types, two types of drugs.

Strobl et al. (2020) : birth-death model, effect of cell turnover.

Spatial models

No PDE models applied to AT, but some models and simulations :

Bacevic & Noble et al. (2017), Gallaher et al. (2018), Li et al. (2017)

Space may be important as :

- boundary growth may justify assumption of competition
- if spatial separation between cells types, low competition
- if resistant cells trapped in tumor core, increases resistance cost
- impacts comparison between continuous AT, intermittent AT, MTD

$\hookrightarrow$ more tomorrow !

Other models

- Evolutionary games including normal cells : West et al. (2018), Kaznatcheev et al. (2019),...
- More optimal control models : Gluzman et al. (2020), Ledzewicz & Schättler (2019),...
- Leader-Follower games (Stankova et al., 2019)
- ...

Current ecology of Adaptive Therapy modeling

Still in Moffitt's gravity field (+ Moffitt's metastases), but expanding

Different styles :

- Simulations of potentially complex models (e.g., Moffitt)
- More or less hard-core optimal control
- Evolutionary game theory models
- Simple maths for pedagogical purposes
- People I do not know very well...

$\hookrightarrow$ need to hear non-Moffit voices + building a community

Some personal messages

To simulators : theoreticians may help to make sense of your results

To hard-core optimal controllers or strong mathematicians :

- Most of us are not able to follow, please translate !
- Finding optimal treatment is great, but comparing containment to MTD is already interesting...
- ... and then easier to vary assumptions to stress-test conclusions.

To theoreticians like me who try to avoid simulations : you're wrong !

What do we need to make better models ? - I

1. Talking, putting our abilities together
2. More data : e.g., please, make Zhang et al. data available !
3. Be precise : e.g., in density-dependent models, are our variables local densities or total population sizes ? May be crucial !
4. Space : PDE models ?
5. Trade-offs between benefits of AT and potential downsides : current models explain why AT could work, not whether AT is likely to work !
6. Risk of adverse event due to large tumor burden (Mistry, 2020)

What do we need to make better models ? - II

1. Partially resistant cells : then not clear that AT superior to MTD
2. More than two sensitivity levels + mutations : $S_1 \to S_2 \to R$
3. Driver mutations, drug-induced resistance
4. Multidrug AT
5. Includes normal cells, immune system...
6. Specificities of prostate cancer ?

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