Mathematical models of adaptive therapy

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Outline

The problem of resistance to treatment

Standard treatment (treating to cure) : "maximum tolerated dose"

Initially great, but often leads to recurrence in a resistant form.

Possible interpretation :

- tumour heterogeneous, contains resistant subclones
- without treatment, resistant cells less fit than sensitive cells
- elimination of sensitive cells allows resistant cells to proliferate

In pest-management, one often tries to "manage" instead of eradicating.

Same approach for cancer $\rightarrow$ adaptive therapy.

Adaptive therapy

- Goal : maximize progression-free survival, not reduce tumor burden
- Use "minimal effective dose", i.e. to maintain tumor stability
- Drugs, dosage, & timing not fixed : response-dependent
- Underlying idea : competition between tumor cells

Practice : dose-modulation or treatment vacation, various cancer types (breast and ovarian cancer in mice, prostate cancer in human patients).

Moffitt advanced prostate cancer trial

Patients with metastatic castration-resistant prostate cancer

Standard of care : Abiraterone at maximal tolerated dose (MTD)

Adaptive therapy trial (Zhang et al., 2017) :

- Measure Prostate Specific Antigen (PSA) level : reference level.
- MTD till PSA drops to 50% of reference level.
- Treatment interrupted till PSA increases to reference level ; iterate.
- Current results : more than doubles median time to progression.

Thyroid cancer trial started in August. Hot topic at Moffitt cancer center.

Some questions

1. What is really happening ? Competitive release ?
2. What is needed for adaptive therapy to work ?
3. How to optimize it ?

   E.g., intermittent high dose versus continuous low dose ?
4. What should we measure to answer these questions ?

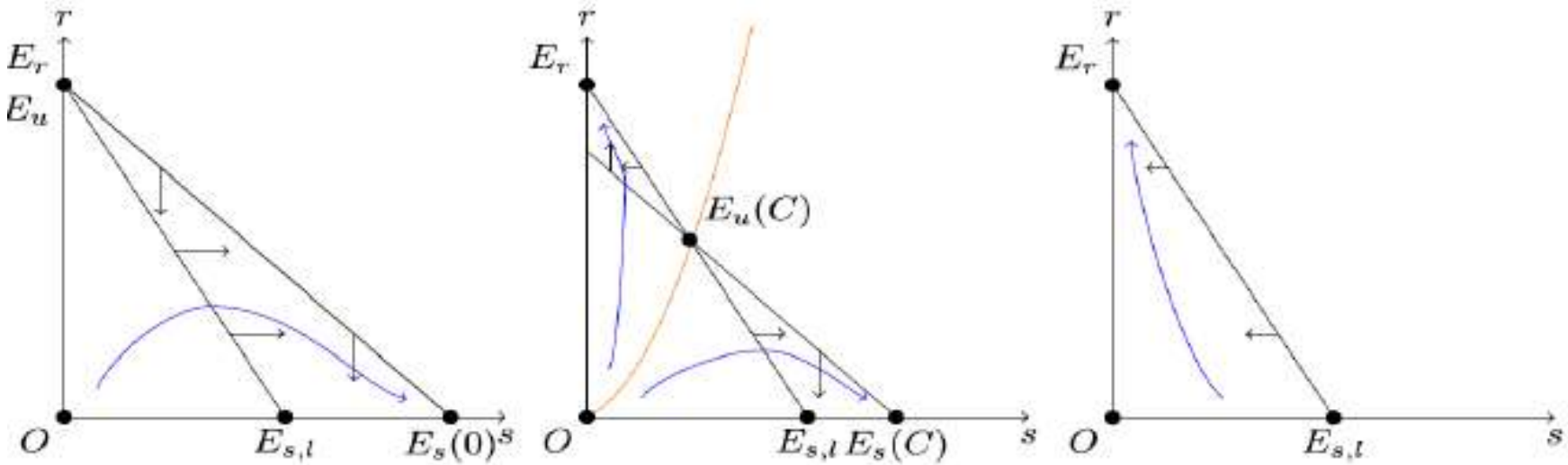
Adaptive therapy : models

- Lotka-Volterra competition (Zhang et al. 2017 ; Carrère 2017 ; Cunningham et al. 2018)
- frequency-dependent models (Silva et al. 2012, Bacevic et al. 2017)
- Gompertzian-growth with dynamic carrying capacity and treatment effect on angiogenesis (Bacevic et al.)
- spatial agent-based models (group in Maastricht, Bacevic et al., Gallagher et al. 2018)
- a few other models I am not sure to understand
- models on related topics : evolutionary cancer modeling, metronomic chemotherapy

Some models : Carrère (2017, JTB) - lung cancer

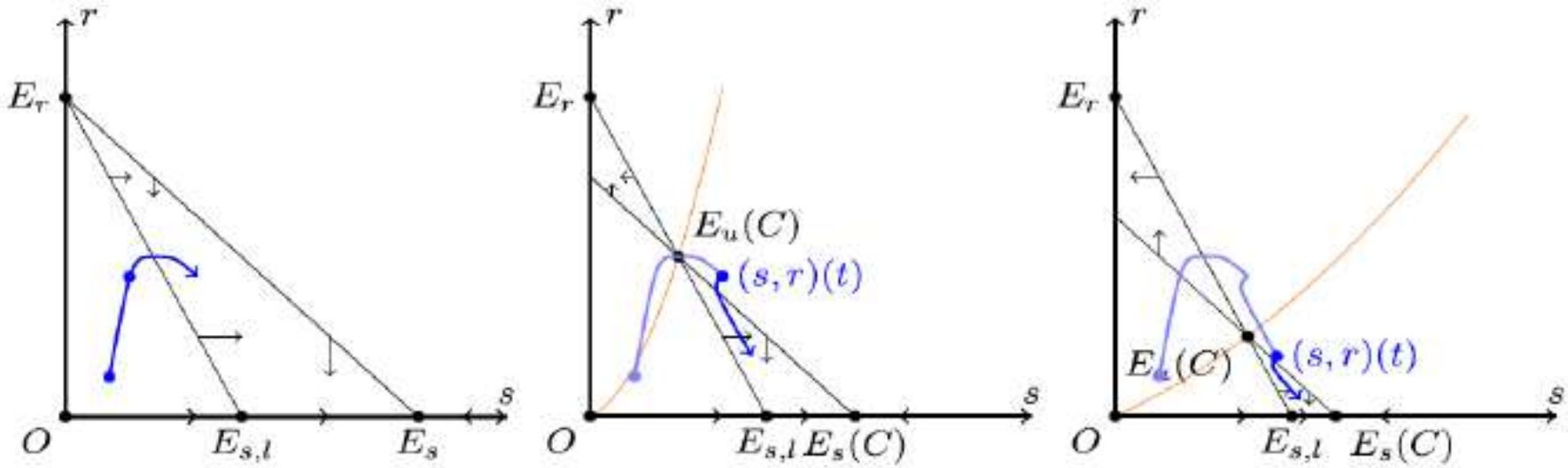
- sensitive and resistant cells, with densities $s(t)$, $r(t)$.
- chemotherapy drug concentration $C(t)$;

$$\begin{aligned} \dot{s}/s &= \rho_s \left(1 - \frac{s + mr}{K}\right) - \alpha C(t) \\ \dot{r}/r &= \rho_r \left(1 - \frac{s + mr}{K}\right) - \beta s \end{aligned}$$



(a) No treatment (b) Weak treatment (c) Strong treatment

Adaptive protocol



(a) Day 1 and 2: the quantity of resistant cells is still growing, so no treatment is applied

(b) Day 3: the system has crossed the designated threshold to start the treatment

(c) Day 4: the treatment value is actualized to bring $E_s(C)$ closer to $E_{s,l}$

+ optimal control for various objectives.

Zhang et al. (2017, Nature Comm.) - prostate cancer

Lotka-Volterra competition between 3 types of cells :

- T^+ (testosterone dependent), TP (testosterone producing) : sensitive
- T^- (testosterone independent) : resistant

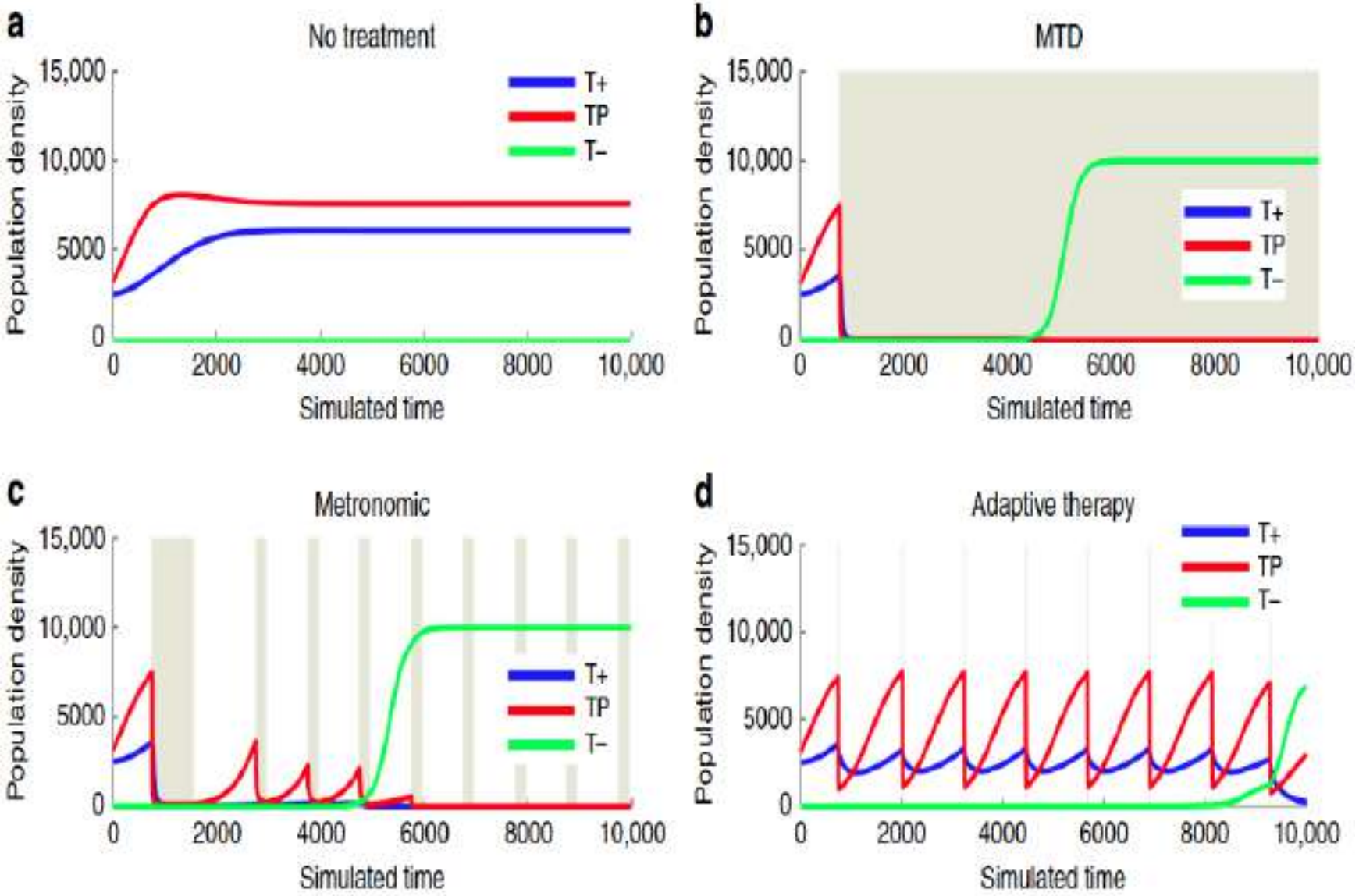
Model may be simplified to two-type model :

$$\begin{aligned} \dot{s}/s &= \rho_s \left(1 - \tfrac{s+\alpha r}{K_s}\right) \\ \dot{r}/r &= \rho_r \left(1 - \tfrac{r+\beta s}{K_r}\right) \end{aligned} \quad \text{with } \alpha, \beta < 1$$

and $K_r = 10000$, $K_s = K_r$ off-treatment, $K_s = K_r/100$ on-treatment

Similar to (Carrère, 2017), but treatment affects carrying capacity

Simulations



What am I trying to do ?

- eventually, models should be more precise, calibrated

- in this infancy stage, even simple models useful

Throughout :

- two types, with population $s(t)$, $r(t)$
- aim : delay tumor progression [time when $s(t) + r(t) > s_0 + r_0$].
- we think of MTD as eradicating the sensitive population : $s(t) = 0$.

Some remarks - I

1) Assume $\dot{r}/r = \rho_r f(s, r)$ with f decreasing in s, sensitive very sensitive

Optimal treatment : keep tumor at initial size. AT superior to MTD.

Intuition : sensitive cells not a problem (in model), and only weapon.

2) Not true if resistant cells only partially resistant (Bacevic et al.)

Intuition : two opposite weapons to fight resistant cells.

3) Zhang et al.'s model may suggest that AT is not interesting.

4) This is true of any Lotka-Volterra model with mild competition.

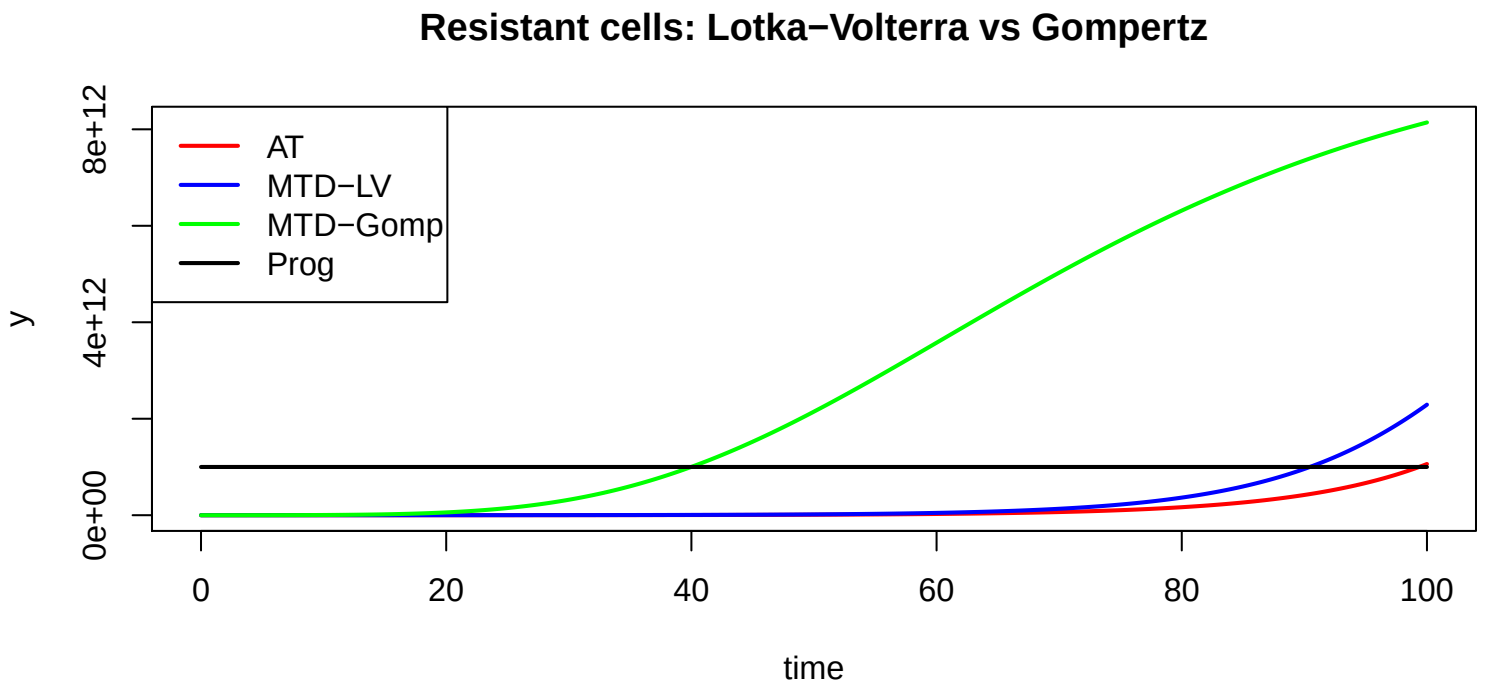
5) Other growth models suggest higher benefit from AT

Simulations : Lotka-Volterra versus Gompertz

Lotka-V : $\dot{r}/r = \rho_r \left(1 - \frac{s+r}{K}\right)$; Gompertz : $\dot{r}/r = \rho_r^{Gomp} \ln\left(\frac{K}{s+r}\right)$

$K = 10^{13}$, $s_0 = 10^{12}$, $r_0 = 10^8$, $\rho_r^{Gomp} = \rho_r(1 - 1/10)/\ln(10)$

AT : maintain tumor size at $K/10$; MTD : $s(t) = 0$



Some remarks - II

6) Another idea : dynamic carrying capacity. E.g., (Hahnfeldt et al. 99) :

$$\dot{K} = bN - dN^{\frac{2}{3}}K$$

7) Importance of resistance cost not obvious

What matters : competition + resistant type initially rare.

8) We need models of heterogeneous tumor growth.

Same overall growth may correspond to very different intra-tumoral dynamics, very different comparisons between AT and MTD.

9) We need competition experiments in harsh, in vivo like conditions.

Conclusions

Adaptive therapy is a meaningful, if somewhat frightening idea.

Thinking about ultimate causes of resistance might be powerful

Initial trials successful, yet scarcity of data and models, and trials crude

Deserves more investigation

We need heterogeneous tumor growth models, competition experiments

Such experiments should try to reproduce in-vivo conditions

Thank you !