

Not Making Matters Worse: Strategies to minimize the evolution of more dangerous cancers in chemotherapy

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Alkylating Agents

Alkylating agents are among the oldest chemotherapy drugs. They work by damaging the DNA of dividing cells in the hopes that:

- Most of the cells so damaged will be cancer cells - reasonable
- Unlike most of the healthy cells, the cancer cells will not be able to repair the damage and will undergo apoptosis in response

The Problem With This Approach

If an unrepaired cancer cell fails to undergo apoptosis → a mutant

- Mutations in cancer cells are undesirable
- Mutations can enhance the effective growth rate of cancer cells
- Other mutation problems

Mutations which enhance effective growth rate of cancer cells might

- Actually increase the intrinsic replication rate
- Lower the repair time for damage inflicted by chemotherapy drugs
- Impair apoptotic response
- Lower the ability to repair damage, which combines with apoptosis effect

Other mutation problems

- Mutations may confer an ability for metastasis
- Easier to treat a genetically uniform mass of cells

Today's model only deals with mutations that don't impact growth rate. Why?

- Enables us to formulate a simple model where there is no movement between cell classes
- This model provides a basic structure which can be modified to include these growth rate-impacting mutations

Stable and Mutator Cells

In this model, we investigate what happens when a tumor contains cells of differing abilities to repair genetic damage.

- For simplicity, we assume that each cell of a tumor falls into one of two classes: the stable class or the mutator class
- By definition, cells of the stable class have a higher probability of repairing genetic damage than do those of the mutator class.
- Apoptotic response assumed to be the same

Model when only stable cells are present

$$\dot{S} = r_{SB}(1-u)S + r_{SB}u(1-\epsilon_S)\alpha S - r_{SB}u\epsilon_S S + 2r_{SB}e^{-d*S*T}u\epsilon_S S(t-T) - d * S^2$$

- Parameters:

u : probability of DNA damage occurring during division

α : probability of damaged cell evading apoptosis

r_{SB} : intrinsic per capita birth rate of stable cells

ϵ_S : probability of a stable cell repairing DNA damage

d : crowding parameter

- Intrinsic death rate, necrotic core

Model With Both Stable and Mutator Cells Present

$$\dot{S} = r_{SB}(1-u)S + r_{SB}u(1-\epsilon_S)\alpha S - r_{SB}u\epsilon_S S + 2r_{SB}e^{-d(S+M)T}u\epsilon_S S(t-T) - d(S+M)S$$

$$\dot{M} = r_{MB}(1-u)M + r_{MB}u(1-\epsilon_M)\alpha M - r_{MB}u\epsilon_M M + 2r_{MB}e^{-d(S+M)T}u\epsilon_M M(t-T) - d(S+M)M$$

- Note that the stable and mutator cells interact solely through competition
- No movement between stable and mutator classes: Mutation assumption
- Although a given cell acquires mutations it continues to be governed by the equation for its class: Mutation assumption
- α : apoptotic response the same

Non-dimensionalized model

$$\frac{dx}{d\tau} = ((1 - u) + u(1 - \epsilon_S)\alpha - u\epsilon_S)x + 2u\epsilon_S e^{-(x+y)T^*}x(\tau - T^*) - (x + y)x$$

$$\frac{dy}{d\tau} = b((1 - u) + u(1 - \epsilon_M)\alpha - u\epsilon_M)y + 2bu\epsilon_M e^{-(x+y)T^*}y(\tau - T^*) - (x + y)y$$

- time unit is $\frac{1}{r_{SB}}$
- population unit is $\frac{r_{SB}}{d}$
- $b = r_{MB}/r_{SB}$

Steady States

There are three steady states: $(s = 0, m = 0)$, $(s = k, m = 0)$,
 $(s = 0, m = l)$

- Stable-only steady state value k satisfies

$$k - ((1 - u) + u(1 - \epsilon_S)\alpha - u\epsilon_S) = 2u\epsilon_S e^{-kT^*}$$

- Mutator-only steady state value l satisfies

$$l - b((1 - u) + u(1 - \epsilon_M)\alpha - u\epsilon_M) = 2bu\epsilon_M e^{-lT^*}$$

When cellular repair is instantaneous,

$$k = k(0) = ((1 - u) + u(1 - \epsilon_S)\alpha + u\epsilon_S)$$

$$l = l(0) = b((1 - u) + u(1 - \epsilon_M)\alpha + u\epsilon_M)$$

Results

- The trivial steady state is unstable for all T^* .
- There is no coexistence steady state.
- Local stability analysis proves that if $k > l$, then the stable cells are locally asymptotically stable while the mutator cells are unstable. If $l > k$, then the reverse is true.
- Simulations suggests that these results hold globally: the cell class which prevails is the one with the larger steady state.
- Both k and l decrease as T^* increases. For certain parameter values, there is a critical repair time T_C at which $k = l$. The stabilities switch when T^* is increased through T_C .

Condition for Stability Switching to Occur

T_C exists iff $l(0) \leq k(0) < l(0) + 2u(\epsilon_S - b\epsilon_M)$.

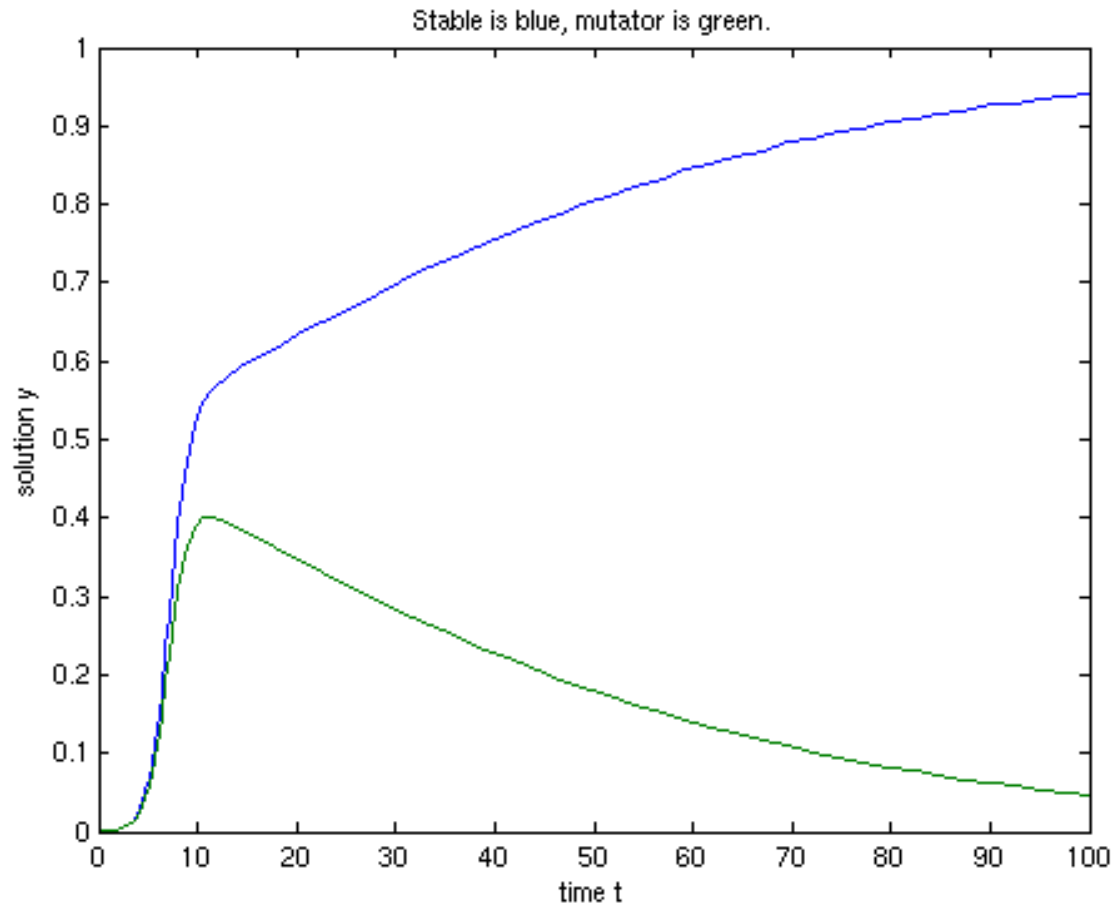
- If $l(0) > k(0)$, then no switching can occur.
- $k(0)$ can exceed $l(0)$ by too great an amount for switching to occur.

Implications for Treatment

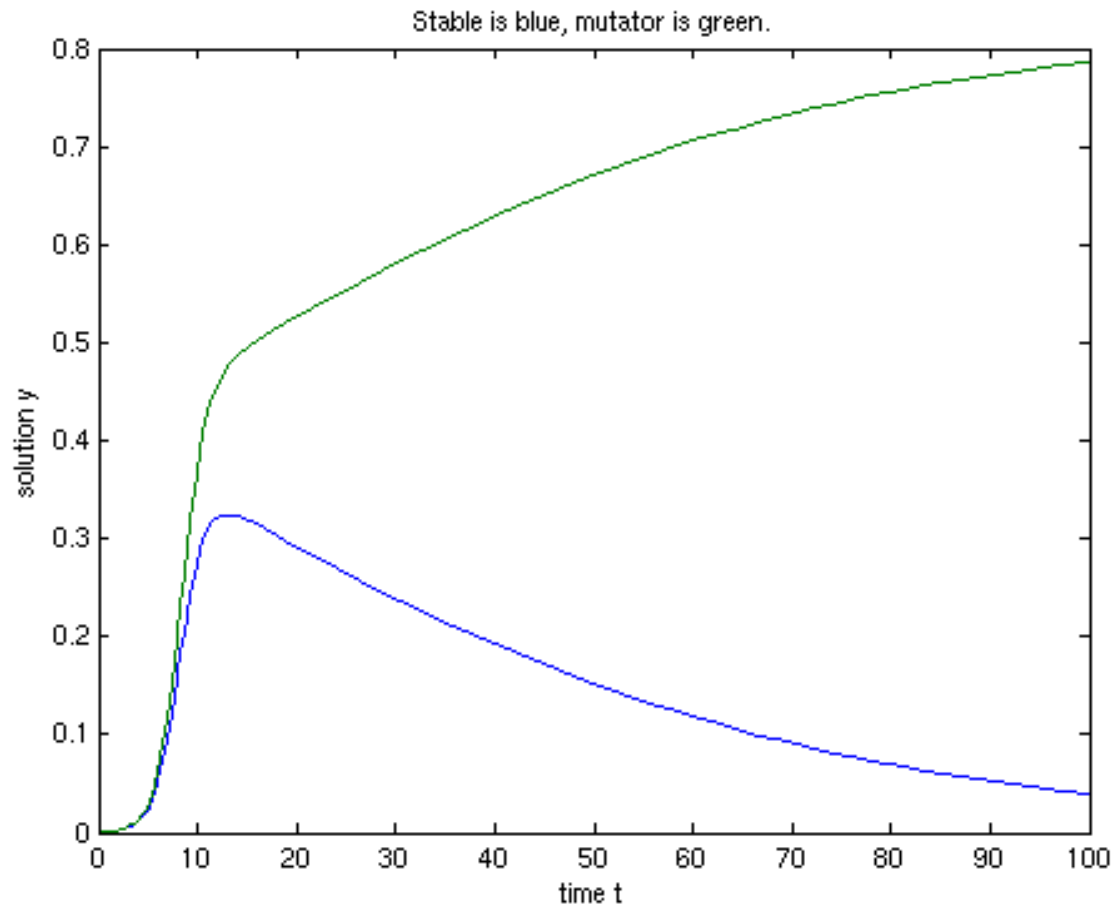
The goal is to shrink the tumor as much as possible (bring it to a lower steady state) while requiring that the stable cells prevail

- If $b \leq 1$ choose $u \leq \frac{k(0)-l(0)}{2(\epsilon_S - b\epsilon_M)}$ and T^* as large as possible

$$T_* = 0, u = 0.5$$



$$T_* = 0.3, u = 0.5$$



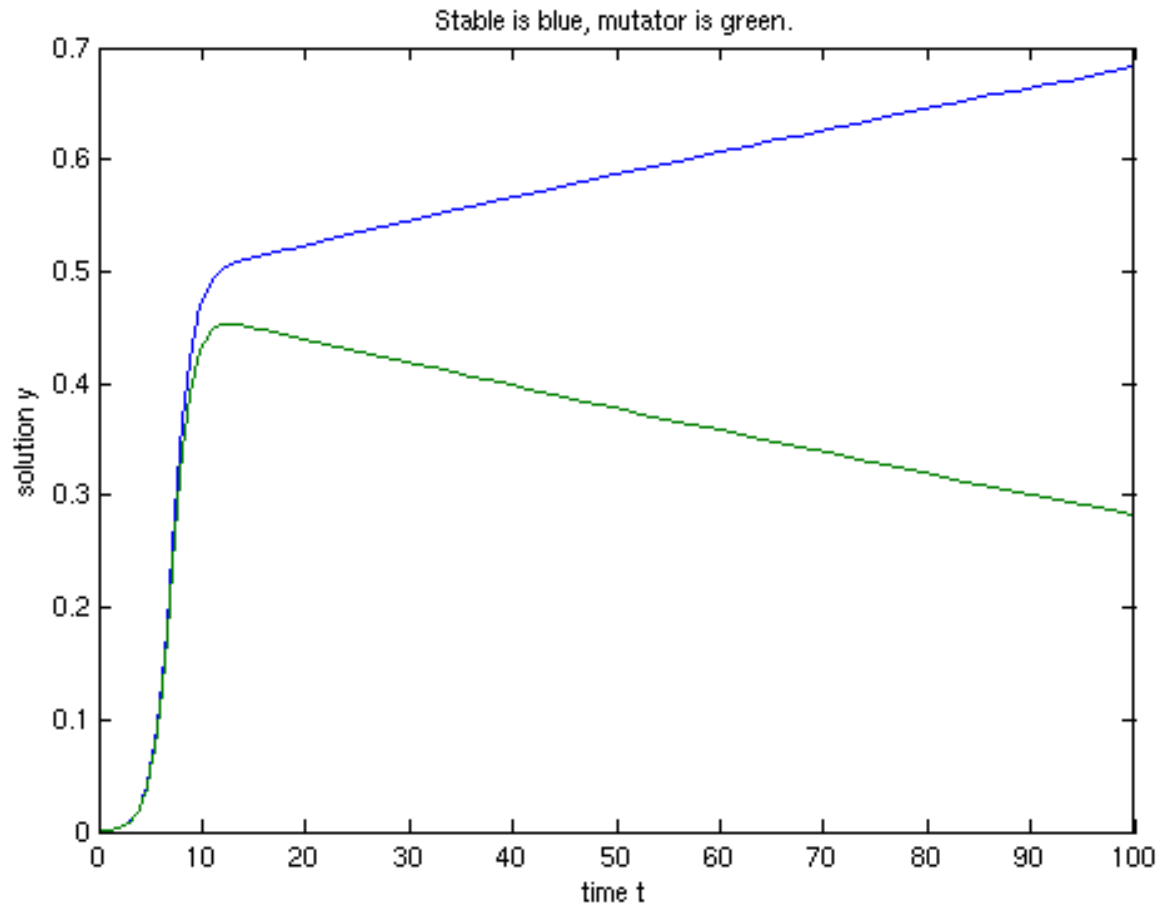
If $b > 1$ and $b < b_C = \frac{(1-\epsilon_S)\alpha + \epsilon_S}{(1-\epsilon_M)\alpha + \epsilon_M}$ then

- choose

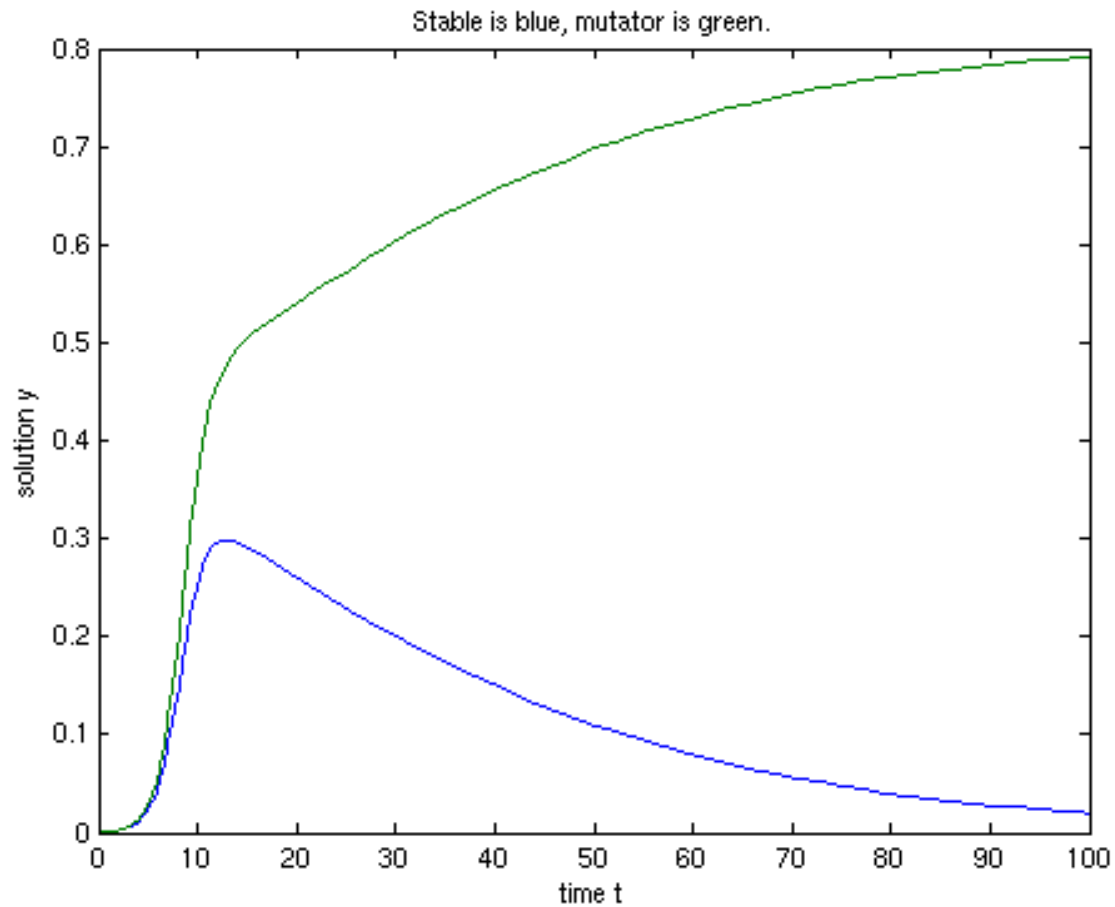
$$u > u_C = \frac{b-1}{(b-1) + (1-\epsilon_S)\alpha - b(1-\epsilon_M)\alpha + \epsilon_S - b\epsilon_M}$$

- Case 1: If can find u such that $u \leq \frac{k(0) - l(0)}{2(\epsilon_S - b\epsilon_M)}$ then choose T^* as large as possible
- Case 2: If this is impossible, choose $T^* < T_C$

$$b = 1.1 < b_C = 1.35, u = 0.4 > u_C = 0.37, T_* = 0$$



$$b = 1.1, u = 0.4, T_* = 0.4$$



If $b > 1$ and $b \geq b_C$ no choice of T^* or u enables the stable cells to prevail. However, by choosing large u and T^* we can minimize the tumor size.

Future Work

- ODE Model? Results very similar to standard ODE competition model. Simpler, might be more realistic.
- “Stable” and “Mutator” are misnomers when α differs: model with many classes characterized by different values of $\epsilon, \alpha, r_B, T^*$. No simple division into “stable” and “mutator” then.
- Movement between groups: mutations that impact effective growth rate.

Thank You

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