Game theoretic approach to modeling cancer metabolism

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Cancer as an ecological system
- Strategies in cell metabolism
- Strategies in cancer metabolism
  - Warburg effect
- Agent-based model
  - Origins of Warburg effect (invasion)
  - Microenvironment toxicity and competition with somatic cells
  - Game of multi-player prisoner’s dilemma
- An ODE model for Warburg effect
  - Based on ideas from invasion ecology
  - Effects of nutrient inflow on system dynamics
- Conclusions
Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults

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BACKGROUND
The influence of excess body weight on the risk of death from cancer has not been fully characterized.

METHODS
In a prospectively studied population of more than 900,000 U.S. adults (404,576 men and 495,477 women) who were free of cancer at enrollment in 1982, there were 57,145

CONCLUSIONS
Increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites.
Primary suspects are hormones produced by adipose tissue that act as tumor-promoting growth factors and immune suppressors (Calle and Kaaks, Nature 2004)

- Adiposity induced changes in levels of sex hormones (esp. oestrogen and progesterone) increase risk of breast and endometrium cancers for women
- Type-II diabetes associated with increased risks of cancers of the colon, endometrium, kidney and pancreas

Is that all?
Cancer as an ecological system

- A tumor is a heterogeneous population of cells that compete for space and nutrients with each other and with somatic cells.
  - The ecosystem is the human body.
  - Whatever the cells’ intrinsic properties may be, they need nutrients to survive before they can proliferate.
Strategies in cell metabolism

- There are in general 2 possible metabolic strategies that cells (any cells) can use:
  - aerobic metabolism
    - very efficient (yielding ≈30 ATP per molecule of glucose)
    - limited by oxygen availability
  - anaerobic metabolism (glycolysis)
    - inefficient in comparison (yielding 2 ATP per molecule of glucose)
    - does not require oxygen
    - lactic acid is a by-product
Aerobic/glycolytic metabolic pathway
Warburg effect

- As tumors outgrow their blood supply and become oxygen deprived, they switch to glycolysis
- However, cancer cells use glycolysis even in the presence of oxygen (aerobic glycolysis, or Warburg effect)
- Why?
Advantages of anaerobic metabolism for cancer cells (Gatenby 2004, 2008)

- In sufficient quantities lactic acid can become toxic to somatic cells
  - Makes glycolytic cells less efficient consumers but better competitors
  - Facilitates metastatic progression (Robey 2009)
- Also, intracellular stores of carbon and phosphorus can be used up by neighboring cells after a cell dies
  - Through releasing lactic acid glycolytic cells not only eliminate competition but also get extra nutrients
An agent-based model: general approach

- Have cells (agents) on a spatial grid
- Each patch on a grid is a microenvironment with resources on it
- Define a set of rules for cells’ interaction with microenvironment and with each other
- See how it turns out
Particular model

- Cells
  - aerobic
    - low energy demands
    - lower tolerance to lactic acid
  - glycolytic
    - high energy demands,
    - release lactic acid when they consume carbon
    - higher tolerance to lactic acid

- Microenvironments characterized by
  - amount of resource (renewable)
  - amount of lactic acid
**Pseudocode for Model Survive-Eat-Reproduce (SER)**

1) Populate cells on the grid (randomly placed, pre-set number of each cell type)
2) Check survival thresholds (food, lactic acid, natural death)
   - intracellular carbon recycled through death
3) Once survived, eat:
   - Aerobic cells subtract less resource from patch
   - Glycolytic subtract more, release lactic acid, which also diffuses to closest neighboring patches
4) After eating, reproduce
Simulation 1

- Aerobic cells (red) - initial 847
- Glycolytic cells (blue) - initial 76
- Acidity reflected in patch brightness
- (movie out1.mov)
Simulation 2

- Aerobic cells (red) - initial 847
- Glycolytic cells (blue) - initial 45
- Acidity reflected in patch brightness
- (movie out2few.mov)
No cell is an island

- One glycolytic cell cannot generate enough lactic acid to become an effective competitor
- Need a core population
- How did it get there?
- So the problem splits into two questions:
  - How could glycolytic cells invade?
  - How many glycolytic cells are enough to jointly get this competitive advantage?
Multi-player prisoner’s dilemma

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<td>(30, 2+minor toxicity)</td>
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- Cells would get a higher competitive advantage if they cooperated (glycolytic-glycolytic strategy) but no cell has an incentive to unilaterally change its metabolic strategy.
- It is the defecting “aerobic-aerobic” strategy that keeps the cells in the tissue from growing uncontrollably.
- Of course, “glycolytic cooperation” does happen. Why? What can cause a change in the stability of the equilibria causing the cells to cooperate?
Goal

- Check whether prolonged availability of excess resources alone could be enough to allow the shift of the composition of the cell population towards glycolytic phenotype.
- or maybe changes in growth/nutrient uptake/death rates are also necessary?
Variables: extracellular carbon, intracellular carbon, and metabolically heterogeneous cell population $x_\alpha$, where $\alpha \to 1$ denotes fully glycolytic cell population.
Modeling parametrically heterogeneous populations

- Assume a population of clones that differ only by a value of some intrinsic parameter
- Distribution of clones within the population can change over time due to system dynamics
  - different clones grow at different rates
  - consequently, mean value of the parameter, which becomes a function of time, changes over time, as well as the distribution
Goals

- Evaluate effects of excessive external carbon inflow on population composition (evaluated through tracking $E_t[\alpha]$) with respect to differences in:
  - Intrinsic growth rates
  - Oxygen availability
  - Intrinsic death rates
  - Resource uptake rates
- Initial distribution of clones within the population is taken to be truncated exponential, heavily skewed towards $\alpha \rightarrow 0$ (vast majority of cell clones at $t=0$ are aerobic)
Assuming that glycolytic cancer clones initially grow exponentially, then if they have even the smallest growth advantage ($r_g > r_a$), they will eventually take over; the question is - how soon?
Without increase in growth rates (even very slight) glycolytic cancer cells cannot invade the tissue (have to have a mutation)
Variations in oxygen availability do have an effect but it’s not extreme.
At this stage of tumor growth high death rates are advantageous: speeds up cell turnover, facilitating invasion and consequently speeding up evolution (argument against cytotoxic therapies)
Upregulated carbon uptake is a secondary adaptation.
Toxicity threshold

- It has been demonstrated that increased nutrient inflow can indeed promote glycolytic phenotype
- At what point do glycolytic cells actually get the competitive advantage from increased environmental toxicity?
  - Modeled through addition of extra death term
Introducing an extra death term to account for mortality from lactic acid allows to model evolutionary suicide.

The “threshold of toxicity” occurs when $E^t[\alpha] \approx 0.1$; the result is robust for different parameter values.
Through changing the environment one can change the stability of equilibria through natural selection alone.

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Environmental changes, such as excess nutrient availability, can compensate for inefficiency of glycolysis and change the stability of the equilibrium from aerobic-aerobic “defecting” strategy to glycolytic-glycolytic “cooperative” strategy.
Conclusions

- Availability of excess nutrients will facilitate invasion by glycolytic clones
  - But just excess carbon is not enough; one must also have differences in growth rates
- Higher death rates are advantageous at this stage
  - Speeds up cell turnover, facilitating invasion
    - an argument against cytotoxic therapies
    - restrain tumor growth rather than try to eliminate it might be better for the patient in the long run
- Upregulation of nutrient transporters is an adaptation rather than the driving force behind glycolytic invasion
  - Targeting them for therapy probably won’t give much
Some nutritional studies

- Some prospective studies have been conducted for both men and women (e.g. Hu et al. (2005), Wright et al. (2007) and others), evaluating causes of mortality correlated to BMI and muscle mass.
- They showed that while there is no overly significant correlation between weight and cancer incidence, cancer mortality was significantly lower for those with higher muscle strength (regardless of adiposity).
  - Perhaps because muscle cells have higher energy demands and “beat” cancer cells to nutrients, thus delaying disease progression.
Acknowledgements

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Some References


Questions? Comments? Suggestions?
Supplementary materials

- On parameter distribution
  - General form for this approach to dimensionality reduction
  - Reduction theorem (from Karev 2010, JMB and Entropy)
  - Why is the method useful?
Dimensionality reduction

Consider the ODEs of the special form

\[
\frac{dP(t,k)}{dt} = P(t,k)(F(t,k) - E^t[F(t,.)])
\]

\[
F(t,k) = \sum_{i=1}^{n} u_i(t, G)\phi_i(k)
\]

\(G(t)=G_1(t),...,G_m(t)\)

is a set of “regulators” of the form

\(G_s(t)=N(t)E^t[g_s]\),

where \(g_s\) are the appropriate weight functions

The initial pdf \(P_0(k)\) and population size \(N(0)\) are given
In applications:

- Functions $\phi_i(k)$ can be interpreted, e.g., as particular phenotype traits that characterize an individual from k-th clone (e.g., having the k-th genotype);
- $u_i(t,G)$ then describe the contribution of the trait to the fitness provided the values of regulators.
Define auxiliary variables through an escort system

\[ \frac{dq_i}{dt} = u_i(t, G^*(t)) \]

where \( q_i(0) = 0, \ i = 1, \ldots, n \), and where \( G^*(t) \) is expressed through the initial pdf

Denote

\[ K_t(a) = e^{\sum_{i=1}^{n} q_i(t) \varphi_i(a)} \]

Then

\[ l(t, a) = l(0, a) K_t(a) \]

\[ P(t, a) = \frac{P(0, a) K_t(a)}{E^t[K_t]} \]

Reduction Theorem
(from Karev 2010, JMB and Entropy)
Why is the Reduction Theorem useful?

- The reduction theorem allows us to reduce the initial system of high or even infinite dimensionality to a low-dimensional system.
- The dimensionality of the initial system may be equal, e.g., to the number of possible genotypes. The dimensionality of the “escort” system is equal to the number of traits, which determine the fitness.