Open problems from math biology: competition between two types of cells

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Introduction

1. Will small cancer continue to grow, or will the immune response shrink it ?
2. Competition between two types of breast cancer cells
3. Competition between two populations of cells during development
4. Competition between Inflammatory T cells and anti-inflammatory T cells
5. Other general models of competition among bacteria,

1, Introduction

Competition is pervasive at every level of life, in particular, in biological processes.

At the cellular level, competition occurs between different populations of cells during development, between different types of immune cells during disease, between normal healthy cells and cancer cells, and between different types of cancer cells.

Here we give some examples, including mathematical models, and associated open problems in PDE

1. Cancer model with normal cells N,
   cancer cells C, and anti-cancer T cells

We first consider the case where $T =$ constant, and take

$$C(r,t) + N(r,t) = 1 \quad \text{for } 0 \le r \le R(t),\ t > 0. \tag{3.11}$$

We assume that C and N satisfy the following equations:

$$\frac{\partial C}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 uC) - \nabla^2 C = \lambda_C C\left(1 - \frac{C+N}{K}\right) - \delta_0 C - \eta C, \tag{3.12}$$

$$\frac{\partial N}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 uN) - \nabla^2 N = \lambda_N N\left(1 - \frac{C+N}{K}\right) - \delta_0 N \tag{3.13}$$

where $K > 1$, $\eta > 0$ Is the killing rate of C by T, and

$$\lambda_C > \lambda_N > \delta_0.$$

We impose no-flux boundary conditions:

$$\frac{\partial C}{\partial r} = 0, \quad \frac{\partial N}{\partial r} = 0 \quad \text{on } r = R(t). \tag{3.14}$$

Adding Eqs. (3.12), (3.13) and using Eq. (3.11), we get

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u) = f(C), \tag{3.15}$$

where

$$f(C) = \lambda_C C(1 - \frac{1}{K}) + \lambda_N (1 - C)(1 - \frac{1}{K}) - \delta_0 - \eta C. \tag{3.16}$$

In healthy state, $C \equiv 0$, $u \equiv 0$. But:

A special solution with $C \equiv 0$, $u \equiv 0$ can occur if and only if $f(0) = 0$ and $N \equiv 1$, and these two conditions hold if and only if

$$f(0) = \lambda_N \left(1 - \frac{1}{K}\right) - \delta_0 = 0 \text{ and (by (3.13)) } N = K\left(1 - \frac{\delta_0}{\lambda_N}\right) = 1.$$

$$\frac{dR}{dt} = u(R(t),t) = \frac{1}{R(t)^2}\int_0^{R(t)} s^2 f(C(s,t))ds.$$

$$-\nu R(t) \le \frac{dR(t)}{dt} \le \nu R(t)$$

for some $\nu > 0$, so that the *a priori* estimates

$$R(0)e^{-\nu t} \le R(t) \le R(0)e^{\nu t} \quad \text{for all } t > 0$$

These estimates can be used to prove the existence of global-in-time solution, and we are interested in the asymptotic behavior the solution, and the existence of steady states and their stability

These two conditions are equivalent, and in the sequel we assume that

$$\lambda_N \left(1 - \frac{1}{K}\right) - \delta_0 = 0. \tag{3.18}$$

From Eq. (3.16) we get

$$f(C) = (\gamma_0 - \eta)C, \tag{3.19}$$

where

$$\gamma_0 = (\lambda_C - \lambda_N)\left(1 - \frac{1}{K}\right) > 0. \tag{3.20}$$

We next rewrite Eq. (3.12) in the form

$$\frac{\partial C}{\partial t} + u\frac{\partial C}{\partial r} - \nabla^2 C = g(C), \tag{3.21}$$

where

$$\begin{aligned} g(C) &= \lambda_C C\left(1 - \frac{1}{K}\right) - \delta_0 C - \eta C - C f(C) \\ &= C(1 - C)(\gamma_0 - \eta). \end{aligned} \tag{3.22}$$

Recalling that $\partial C/\partial r = 0$ on the boundary $r = R(t)$, we can compare $C(r,t)$ with solutions $\hat{C}(t)$ of the ODE system

$$\frac{d\hat{C}}{dt} = \hat{C}(1-\hat{C})(\gamma_0 - \eta), \quad \hat{C}(0) = C_0, \tag{3.23}$$

If

$$0 < C_{10} \le C(r,0) \le C_{20} < 1 \quad \text{for } 0 \le r \le R(0),$$

and $\hat{C}_j(t)$ is the solution of (3.23) with $C_0 = C_{j0}$, then

$$\hat{C}_1(t) \le C(r,t) \le \hat{C}_2(t) \quad \text{for } 0 \le r \le R(t),\ t > 0.$$

and use this in the equation

$$\frac{dR}{dt} = u(R(t), t) = \frac{1}{R(t)^2} \int_0^{R(t)} s^2 f(C(s,t)) ds.$$

or

$$\frac{dR(t)}{dt} = \frac{\gamma_0 - \eta}{R^2(t)} \int_0^{R(t)} s^2 C(s,t) ds < 0,$$

to prove the following theorem:

THEOREM 3.1. *Consider the system (3.11)-(3.14) with* λ_N *as in Eq. (3.18) and with initial condition* $0 < C(r,0) < 1$ *for* $0 \le r \le R(0)$. *Then the following holds: (i) if* $\eta < \gamma_0$ *then* $R(t) \to \infty$ *and* $C(r,t) \to 1$ *uniformly as* $t \to \infty$; *(ii) if* $\eta > \gamma_0$ *then* $\frac{dR(t)}{dt} < 0$, *and* $\frac{dR(t)}{dt} \to 0$ *and* $C(r,t) \to 0$ *uniformly as* $t \to \infty$.

The above method of comparing with an ODE equation extends to any system with zero flux boundary condition

Open problem

Extend Theorem 3.1 to the case on non-zero flux boundary conditions

$$b\frac{\partial C}{\partial r} + \alpha C = 0, \quad b\frac{\partial N}{\partial r} + \alpha N = N_0 \quad \text{for some } \alpha > 0$$

2. Two types of breast cancer cells are in competition

scientific reports

OPEN

Frequency-dependent interactions determine outcome of competition between two breast cancer cell lines

Audrey R. Freischel[1,2,3✉], Mehdi Damaghi[1,3✉], Jessica J. Cunningham[1,2], Arig Ibrahim-Hashim[1], Robert J. Gillies[1], Robert A. Gatenby[1,2] & Joel S. Brown[1,2]

Scientific Reports | (2021) 11:4908 | https://doi.org/10.1038/s41598-021-84406-3 nature portfolio

Lotka-Volterra equation: the parameters are determined to fit the data

$$\begin{cases} \frac{dN_1}{dt} = N_1 r_1 \left(1 - \frac{N_1 + \alpha N_2}{K_1}\right) \\ \frac{dN_2}{dt} = N_2 r_2 \left(1 - \frac{N_2 + \beta N_1}{K_2}\right) \end{cases}$$

Problem

It will be interesting to add diffusion and advection as we did in the previous model with

C = N1 and N = N2 but without T cell (i.e. eta=0)

The RHS of each equation is, of course, different than in the previous system

The above paper has lots of clinical data

3. Two populations of cells in competition; example taken for Drosophila during development

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Competitive Interactions Between Cells: Death, Growth, and Geography

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Cells with different metabolic rates

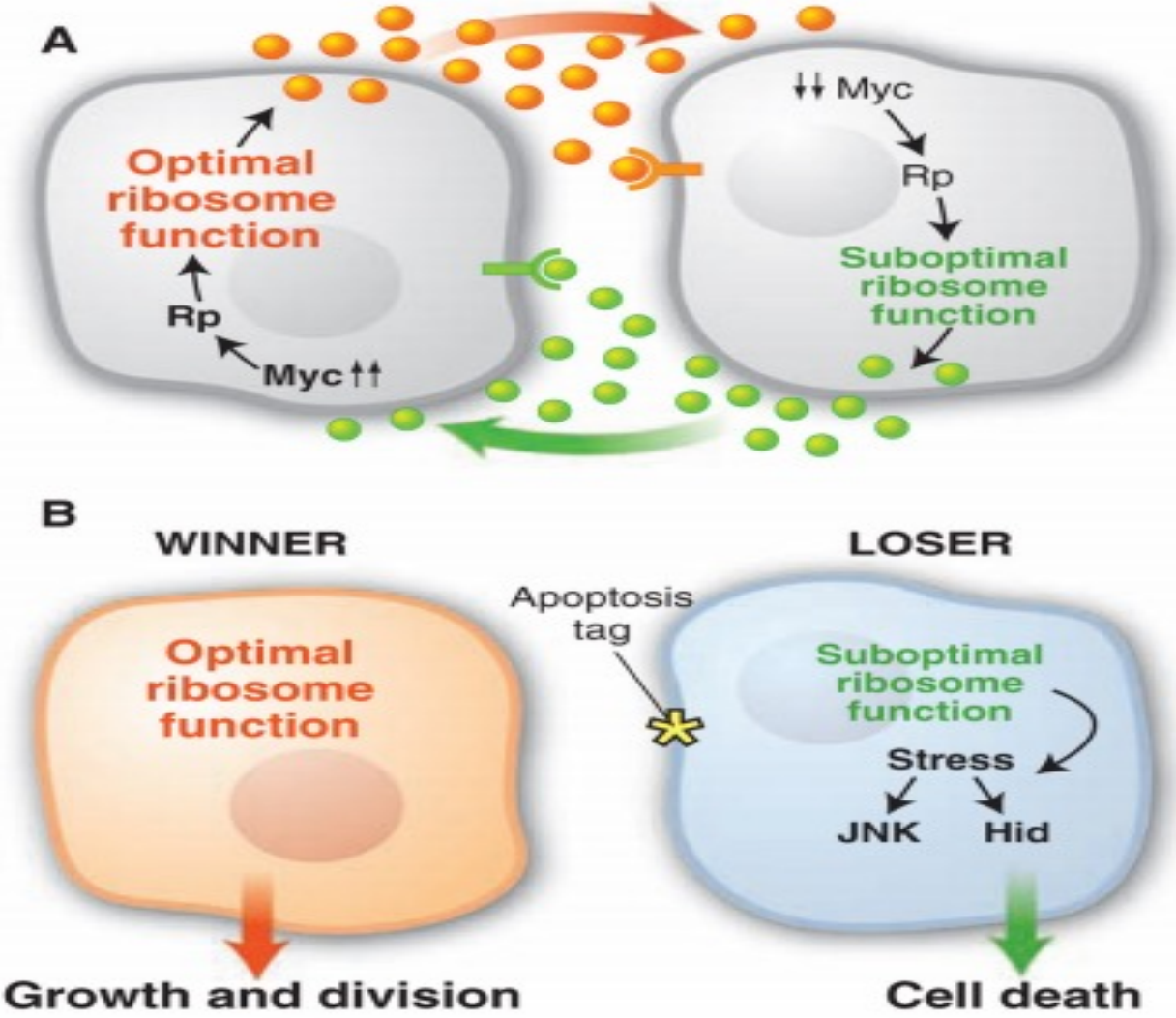

Fig. 1.
A model of cell competition. (**A**) Neighboring epithelial cells recognize relative differences in ribosome function through a sensing mechanism that may involve the production of secreted factors by each cell (orange and green dots). (**B**) Once a difference is sensed, cells acquire "winner" or "loser" status, determined by their relative ribosome function. Loser cells sense stress and activate the JNK signaling pathway and expression of the proapoptotic factor, Hid. Hid induces apoptosis and leads to loser-cell death. Winner cells, with optimal ribosome function, are stimulated to proliferate faster. They also can activate genes required for cell engulfment, leading them to engulf dying loser cells (asterisk). Arrows depict genetic relationships rather than direct biochemical interactions.

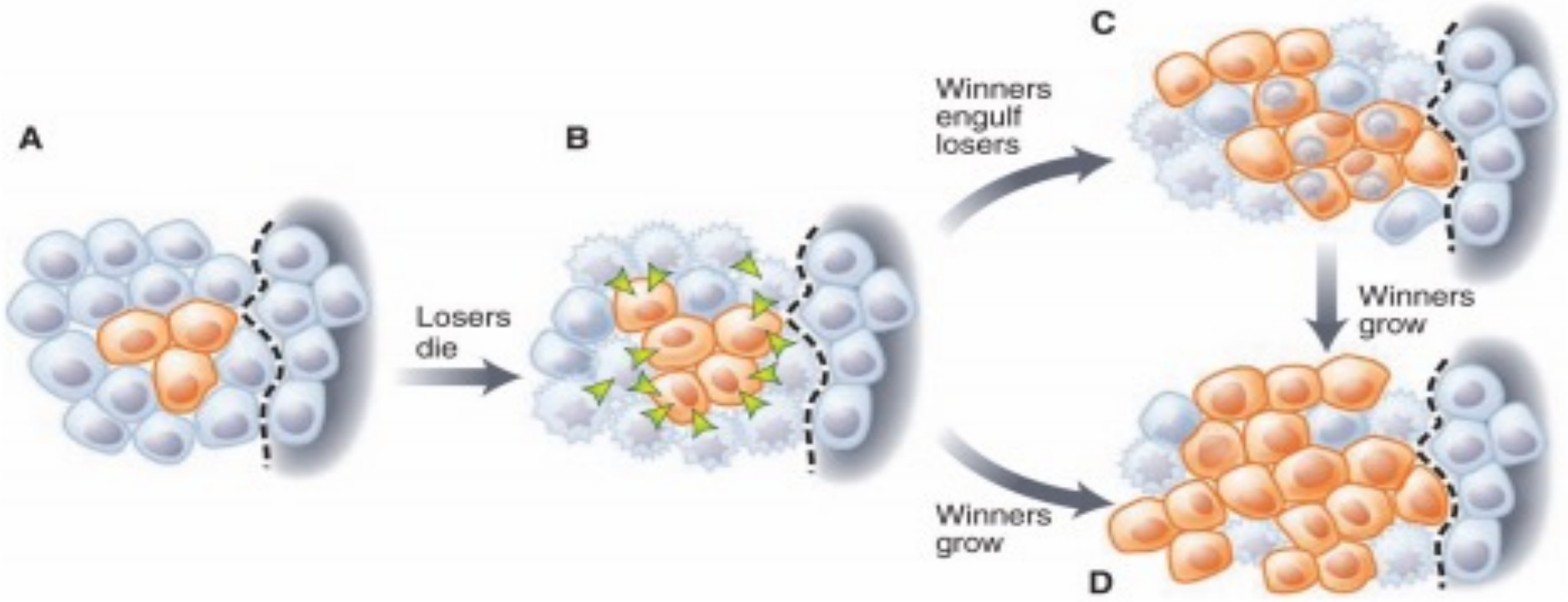

Fig. 2.
Cells are insulated from competition by compartment boundaries. (**A**) Cell competition occurring on one side (left) of a compartment boundary (dotted line) does not affect cells on the other side (right). Gray cells, losers; orange cells, winners. (**B**) Local interactions between cells identify relative metabolic status, triggering apoptosis in losers. Signals from dying cells (arrowheads) may stimulate the growth of winner cells. Cells to the right of the compartment boundary are completely protected. (**C**) Loser cells can be engulfed by winner cells. This process promotes winner-cell proliferation. (**D**) Winner cells expand their territory at the expense of loser cells. However, this expansion is limited to one compartment, because cells in the opposite compartment (right of the dotted line) remain insulated. The geographic limits of competition help stabilize organ size.

Model equations

$$P = \text{loser} \quad Q = \text{winner} \quad S = \text{signal}$$

$$\begin{cases} \frac{\partial P}{\partial t} + \theta \mathrm{div}(P\vec{u}) - \nabla^2 P = \lambda_1 P\left(1 - \frac{P+Q}{K}\right) - d_1(1+S)P & \text{in } \Omega, \\ \frac{\partial Q}{\partial t} + \theta \mathrm{div}(Q\vec{u}) - \nabla^2 Q = (\lambda_1 Q + \epsilon P)\left(1 - \frac{P+Q}{K}\right) - d_1 Q & \text{in } \Omega, \\ \frac{\partial S}{\partial t} - \delta \nabla^2 S = \lambda_2 Q - d_2 S, & \text{in } \Omega, \end{cases}$$

with appropriate boundary conditions (such as $\alpha \frac{\partial X}{\partial n} + (1-\alpha)X = 0$) and parameters

$$\delta \sim 10^3, \quad d_1 \sim 1, \quad d_2 \sim 10, \quad \lambda > d_1, \quad \lambda_2 > d_2, \quad \epsilon > 0.$$

Q cells eat dying P cells, so we model it in one of two ways:

1. P + Q = 1 and e = 0 and then we get a free boundary problem as in the case of cancer and normal cells, part of the boundary is fixed, or
2. Taking e > 0 and theta = 0 in fixed domain

Open problem

Study the asymptotic solution as $t \to \infty$

4. Competition between effective T cells and regulatory T cells, mediated by Interleukin IL-2

Effective T cells (T_1) kill pathogen, but cause toxicity; T regulatory cells (T_r) control T_1 in order to reduce toxicity

Animals who do not have IL-2, suffer from many autoimmune diseases

REVIEW article

Front. Immunol., 05 September 2012 |
https://doi.org/10.3389/fimmu.2012.00268

Competition for IL-2 between regulatory and effector T cells to chisel immune responses

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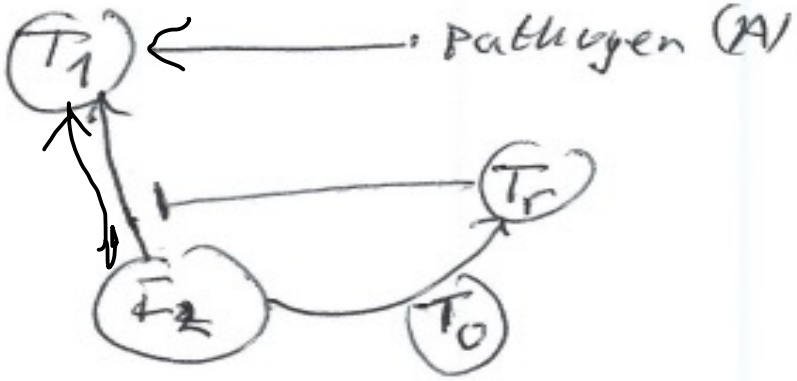
- T_1 cells are activated by the presence of pathogen (A)
- T_1 cells secrete cytokine IL-2 (I_2)
- I_2 activates naive cells T_0 to become T regulatory cells, T_r.
- I_2 makes T_1 cells more proliferative, but T_r blocks this over-proliferation.



Model equations

$$(S)\begin{cases} \frac{\partial T_1}{\partial t} - \nabla^2 T = A + \lambda_1 \frac{T_1}{1+T_r/K} I_2 - d_1 T_1 & \text{in } \Omega, \\ \frac{\partial T_r}{\partial t} - \nabla^2 T_r = \lambda_2 T_0 I_2 - d_1 T_r & \text{in } \Omega, \\ \frac{\partial I_2}{\partial t} - \delta \nabla^2 I_2 = \lambda_3 T_1 - \lambda_4 T_1 I_2 - \lambda_S T_0 I_2 - d_2 I_2 & \text{in } \Omega, \end{cases}$$

with boundary conditions

$$\beta_i \frac{\partial X_i}{\partial n} + (1-\beta_i) X_i = 0 \quad \text{on } \partial\Omega, \quad X_i = T_1, T_r, I_2.$$

Open problems

Problem 1. Take $\beta = 1$ so the PDEs become ODEs for spatially homgoeneous solutions, and

$$0 < A < 1, \quad d_1 = 0.1, \quad d_2 = 1, \quad K = 1, \quad T_0 = 1.$$

Show that given any $0 < A < 1$ and $\lambda_1, ..., \lambda_5$, there exists unique steady state solution (T_1^0, T_r^0, I_2^0) with $T_r^0 > 0$, $I_2^0 > 0$ and any solution of the system (S) converges to this solution as $t \to \infty$.

Problem 2. What if $0 \leq \beta < 1$?

6. Other competitions

Computation of mutual fitness by competing bacteria

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Contributed by Robert H. Austin, October 28, 2008 (sent for review August 20, 2008)

Competing populations in shared spaces with nonrenewable resources do not necessarily wage a battle for dominance at the cost of extinction of the less-fit strain if there are fitness advantages to the presence of the other strain. We report on the use of nanofabricated habitat landscapes to study the population dynamics of competing wild type and a growth advantage in stationary phase (GASP) mutant strains of *Escherichia coli* in a sealed and heterogeneous nutrient environment. Although GASP mutants are competitors with wild-type bacteria, we find that the 2 strains cooperate to maximize fitness (long-term total productivity) via spatial segregation: despite their very close genomic kinship, wild-type populations associate with wild-type populations and GASP populations with GASP populations. Thus, wild-type and GASP strains avoid each other locally, yet fitness is enhanced for both strains globally. This computation of fitness enhancement emerges from the local interaction among cells but maximizes global densities. At present we do not understand how fluctuations in both spatial and temporal dimensions lead to the emergent computation and how multilevel aggregates produce this collective adaptation.

biophysics | competition | ecology | microbiology

the rpoS gene typically, which codes the σ_S factors of the RNA polymerase (15–17).

The switching of σ factors (from log phase σ_{38} to stationary phase σ_S) triggers the entry into stationary phase. We compared monoculture populations with 2-strain (WT and GASP) competitive communities and compared total biomass productivity across experiments.

Multispecies communities can be described by a simple Lotka–Volterra equation (Eq. **1**), where the bacterial density of strain i is $\rho_i(t)$, the effective growth rate is r_i, and the influence of the strains on each other is characterized by the (community) matrix element $J_{i,j}$ that represents the ecological coupling between strains and their environment (18).

$$\frac{d\rho_i}{dt} = r_i \rho_i \left(1 - \sum_j J_{i,j} \rho_i\right) \qquad [1]$$

In spatially extended systems, however, parameters of Eq. **1** vary in space and time at multiple scales in a complex manner. Critical scales are a result of the landscape structure and interactions between individuals (19, 20) and thus are difficult to determine

ORIGINAL RESEARCH article
Front. Microbiol., 22 September 2020 | https://doi.org/10.3389/fmicb.2020.572487

Modeling Competitive Mixtures With the Lotka-Volterra Framework for More Complex Fitness Assessment Between Strains

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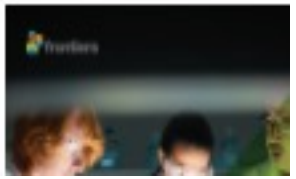


2.2. A More Complex Alternative: The Lotka-Volterra Competition Model

One way to accommodate more complexity and generality into the system, is to develop an alternative approach for this type of competitive mixture data. We propose the next-order approximation away from the exponential model: a dynamic model based on the well-known Lotka-Volterra competition equations (Volterra, 1926), and interpret the transmission event as a snapshot from such competition dynamics. Let $n_1(t)$ and $n_2(t)$ be the number of virions of strain 1 and 2, respectively, at time t in the recipient host. They change with time according to the following equations:

$$\frac{dn_1}{dt} = r_1 n_1 - c_{11} n_1^2 - c_{12} n_1 n_2$$

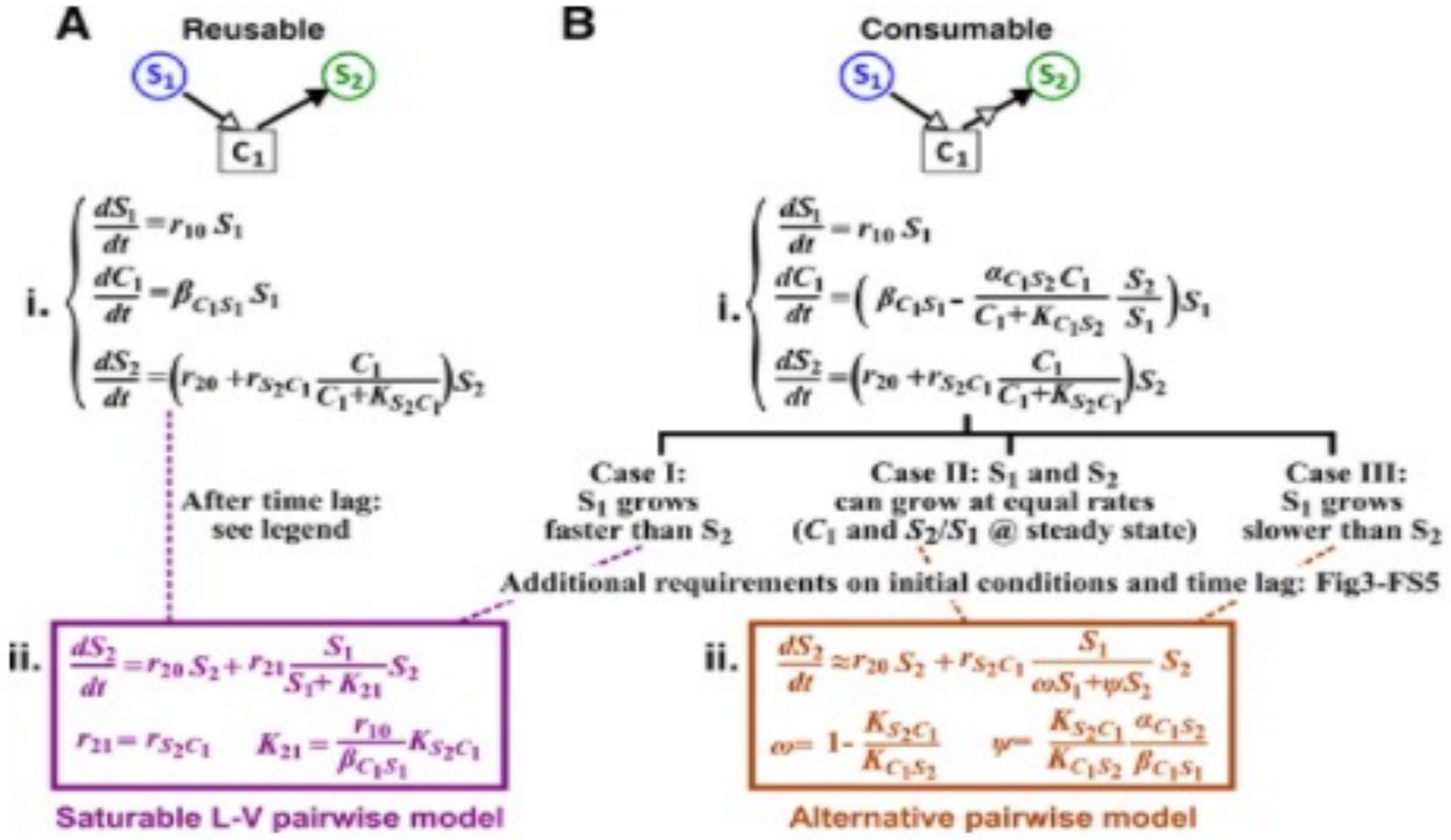
$$\frac{dn_2}{dt} = r_2 n_2 - c_{22} n_2^2 - c_{21} n_1 n_2$$

Computational and Systems Biology, Ecology

Lotka-Volterra pairwise modeling fails to capture diverse pairwise microbial interactions

Babak Momeni, Li Xie, Wenying Shou see all »
Boston College, United States; Fred Hutchinson Cancer Research Center, United States see all »

Research Article · Mar 28, 2017


A
Reusable
S1
S2
C1
i.
$\frac{dS_1}{dt} = r_{10} S_1$
$\frac{dC_1}{dt} = \beta_{C_1 S_1} S_1$
$\frac{dS_2}{dt} = \left(r_{20} + r_{S_2 C_1} \frac{C_1}{C_1 + K_{S_2 C_1}}\right) S_2$
After time lag:
see legend
ii.
$\frac{dS_2}{dt} = r_{20} S_2 + r_{21} \frac{S_1}{S_1 + K_{21}} S_2$
$r_{21} = r_{S_2 C_1}$ $K_{21} = \frac{r_{10}}{\beta_{C_1 S_1}} K_{S_2 C_1}$
Saturable L-V pairwise model
B
Consumable
S1
S2
C1
i.
$\frac{dS_1}{dt} = r_{10} S_1$
$\frac{dC_1}{dt} = \left(\beta_{C_1 S_1} - \frac{\alpha_{C_1 S_2} C_1}{C_1 + K_{C_1 S_2}} \frac{S_2}{S_1}\right) S_1$
$\frac{dS_2}{dt} = \left(r_{20} + r_{S_2 C_1} \frac{C_1}{C_1 + K_{S_2 C_1}}\right) S_2$
Case I:
S1 grows
faster than S2
Case II: S1 and S2
can grow at equal rates
(C1 and S2/S1 @ steady state)
Case III:
S1 grows
slower than S2
Additional requirements on initial conditions and time lag: Fig3-FS5
ii.
$\frac{dS_2}{dt} \approx r_{20} S_2 + r_{S_2 C_1} \frac{S_1}{\omega S_1 + \psi S_2} S_2$
$\omega = 1 - \frac{K_{S_2 C_1}}{K_{C_1 S_2}}$ $\psi = \frac{K_{S_2 C_1}}{K_{C_1 S_2}} \frac{\alpha_{C_1 S_2}}{\beta_{C_1 S_1}}$
Alternative pairwise model