Modeling of cancer virotherapy with recombinant measles viruses

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SMB, Toronto, 2008

Outline

Abstract

The Edmonston vaccine strain of measles virus has potent and selective activity against a wide range of tumors. Tumor cells infected by this virus or genetically modified strains express viral proteins that allow them to fuse with neighboring cells to form syncytia that ultimately die. Moreover, infected cells may produce new virus particles that proceed to infect additional tumor cells. We present a model of tumor and virus interactions based on established biology and with proper accounting of the free virus population. The range of model parameters is estimated by fitting to available experimental data. The stability of equilibrium states corresponding to complete tumor eradication, therapy failure and partial tumor reduction is discussed. We use numerical simulations to explore conditions for which the model predicts successful therapy and tumor eradication. The model exhibits damped, as well as stable oscillations in a range of parameter values. These oscillatory states are organized by a Hopf bifurcation.

Virotherapy studies

- Adenovirus: head and neck cancer (Nemunaitis et al., 2001)
  Metastatic colon cancer (Reid et al., 2001, 2002)
- Newcastles diseases: *various* (Pecora et al., 2002)
- Edmonston vaccine strain of measles:
  - non-Hodgkin lymphoma (Grote et al., 2001)
  - multiple myeloma (Peng et al., 2002)
  - ovarian carcinoma (Peng et al., 2002)
  - cerebral glioma (Phyong et al., 2003)
  - breast carcinoma (McDonald et al., 2006)
- Phase I and II clinical trials have investigated safety.
  Suboptimal delivery and low doses limit efficacy.

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Virotherapy of measles

- Virus has (or engineered to have) selective activity against tumor cells.
  - + Most tumor cells over express receptor CD46.
  - + No harmful effects on normal tissue.
- Infected tumor cells become virus factories.
  - + Cell death releases virions for reinfection.
  - + Replication of infected cells is small.
- Infected tumor cells fuse with “healthy" tumor cells and eventually die.
  - + Fusion $\gg$ lysis. (Peng et al. 2002, Anderson et al. 2004.)
  - + Syncytia die in (2-3 days).
- In vivo monitoring via bio-markers detected in the blood or molecular imaging via iodide isotopes preferentially absorbed by the tumor.

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Myeloma data

- In vivo experiments by Dingli, et al., 2004.
  - + Human myeloma xenografts grown in immunodeficient mice.
  - + Data obtained for the size of untreated tumors.
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- Population interactions require mathematical models.
- Each *important* biological process is represented by a different term in the equations.
  ASSUMPTIONS
  - Which processes are unimportant and not included?
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  How well does the model (simulated or analytical results) match the physical system?
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  - + Therapy optimization.
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Generalized Logistic growth of tumor

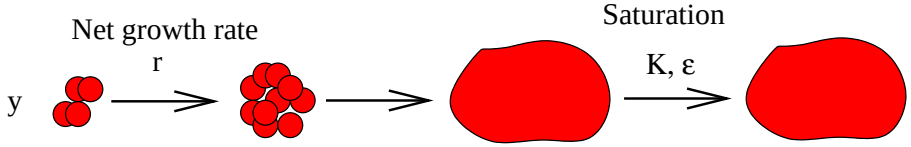
Bertalanffy-Richards

$$\frac{dy}{dt} = ry\left[1 - \frac{(y+x)^{\epsilon}}{K^{\epsilon}}\right] - \kappa yv - \rho xy$$

$$\frac{dx}{dt} = \kappa yv - \delta x$$

$$\frac{dv}{dt} = \alpha x - \omega v - \kappa yv$$

Generalized Logistic growth of tumor



Viral infection of tumor

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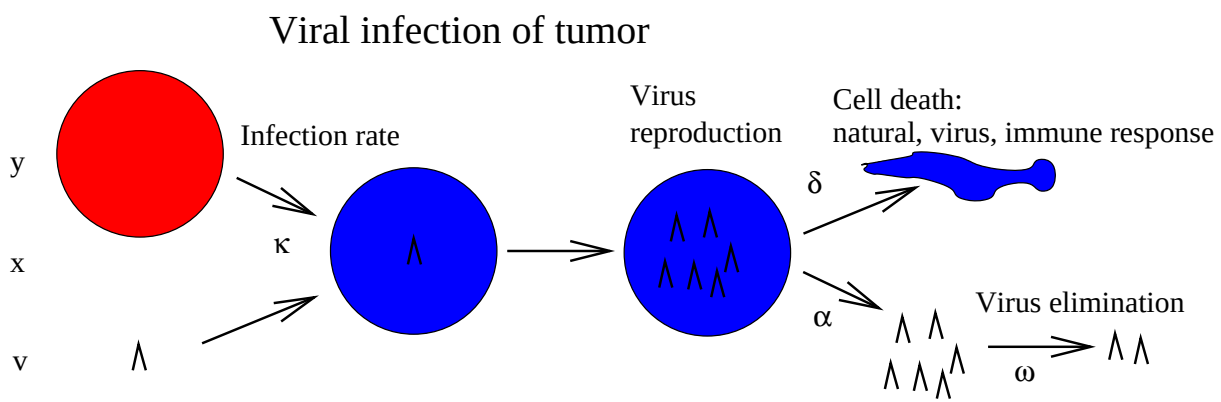

Cell death and virus release

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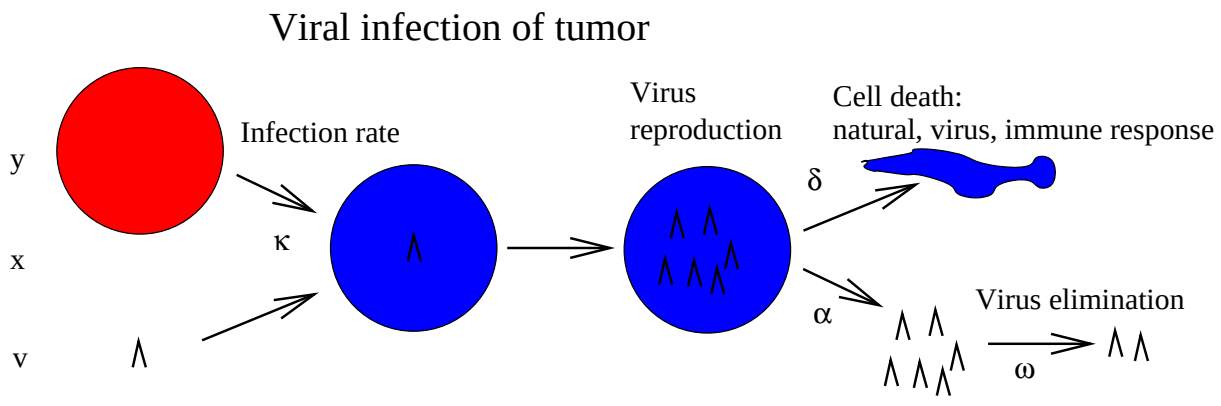

Tumor cell fusion

Entension of models by Wodarz et al. (2001, 2003, 2005).

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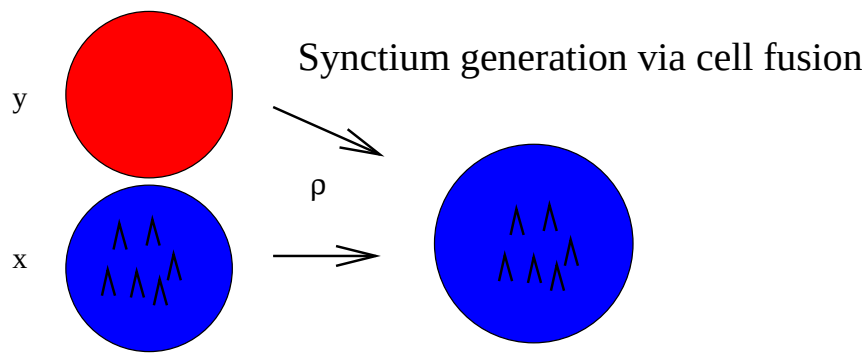

Rate equations and parameters

$$\begin{aligned}
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\end{aligned}$$

r	effective growth rate of uninfected cells (day^{-1})
K	carrying capacity (in 10^6 cells)
κ	infection rate constant (per day per 10^6 cells or virions)
ρ	rate constant of cell fusion (per day per 10^6 cells)
δ	effective death rate constant of infected cells (day^{-1})
ω	rate constant of virus elimination (day^{-1})
α	virus production rate constant (virions per day per cell)

Rate equations and block diagram

$$\frac{dy}{dt} = ry\left[1 - \frac{(y+x)^{\epsilon}}{K^{\epsilon}}\right] - \kappa yv - \rho xy$$

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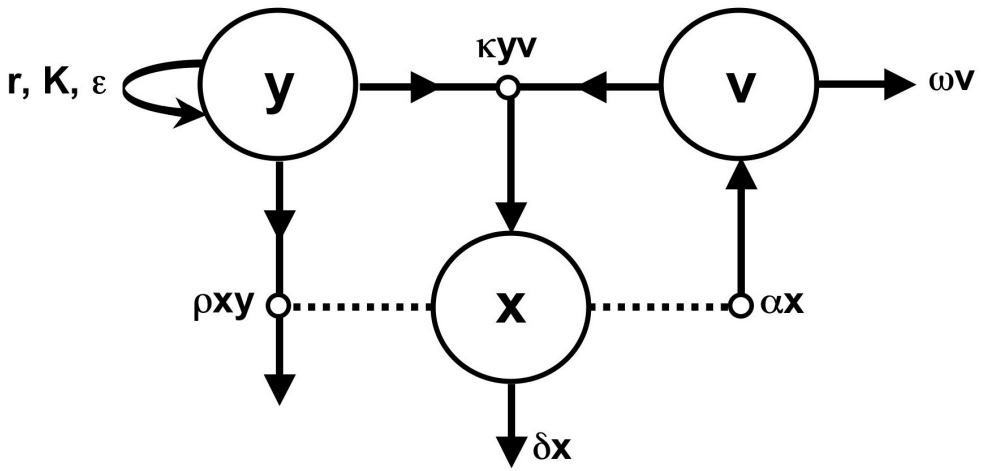

Total tumor size u.

- $u = x + y$: total tumor size.
- $u < 10^{-6}$: Absolute tumor eradication = less than one cell.
- $u = 1$: Experimental limit of tumor detection $\approx 10^6$ cells.
- $t = 1000$: Max. lifetime of mouse.
- $u(1000) \leq 1$: “Successful" therapy.

Experimental limitations and practicalities must be acknowledged.

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Therapy failure or success

- $u = 0$: Tumor eradication $=$ *success*.
  UNSTABLE: $u \not\to 0$
- $u = K$: Saturation and therapy *failure*.
- $u < K$: Reduced tumor size: *Partial success*.
- Exchange of stability between success and *partial success*.

$$\delta\omega = (\alpha - \delta)\kappa K$$

An increase in the infection rate of virus production (κ), or a decrease in the rate of virus elimination (ω), increases the effectiveness of therapy. Failure $\Rightarrow$ partial success.

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Least squares and Monte Carlo

- Data: untreated tumors and virotherapy at $t = 15$ days.
  Tumor size units: 1 $mm^3 \approx 10^6$ cells.
- Weighted non-linear least-squares.
- Parameter error estimates:
  Monte carlo simulations with parameter “noise" based on experimental error bars.

fit	κ	δ	α	ω	ρ	χ^2
a	0.000959	0.512	0	0	0.215	1.0155
S.D.	0.000861	0.276	0.026	0.021	0.116	
b	0.000958	0.513	0.001	0.001	0.216	1.0175
c	0.000448	0.309	0.001	0.3	0.608	1.2839
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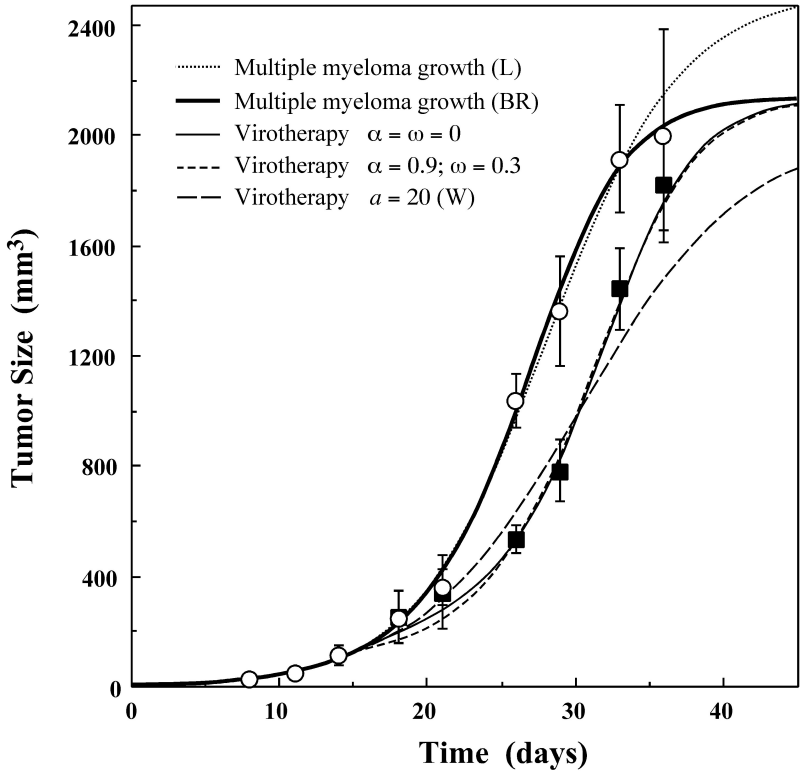
Model vs. untreated-tumor data

Data (circles) compared to:

- Gompertz
- Logistic
- Generalize-Logistic
  $r \approx 0.21$
  $K \approx 2140$
  $\epsilon \approx 1.65$)



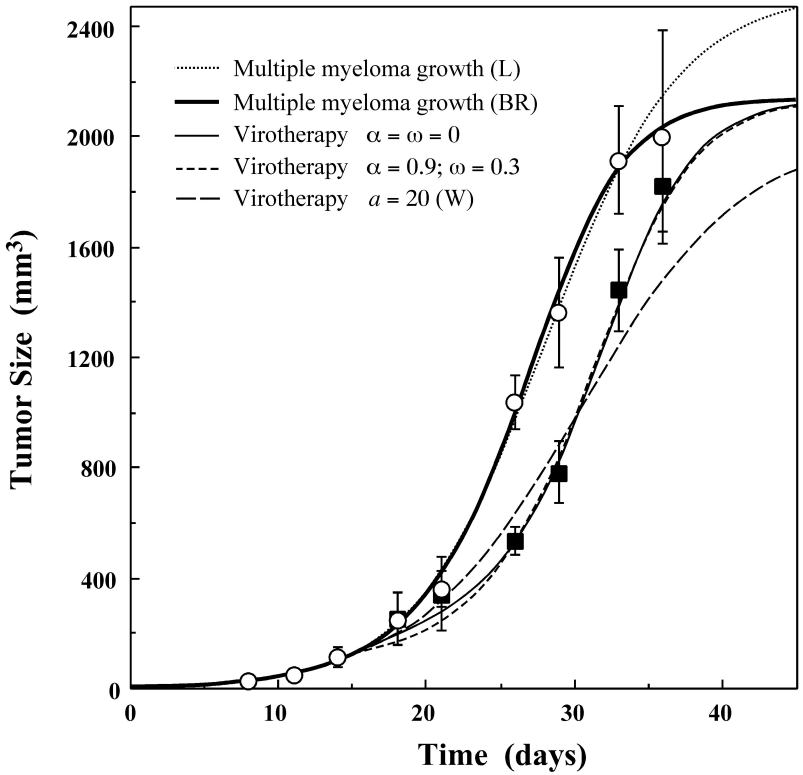
Model vs. virotherapy data

Data (squares). Find: $\kappa,\ \rho,\ \delta\ ,\alpha\ ,\omega$

- Zero free virus production and elimination.
  - Best fit: $\alpha = 0$, $\omega = 0$.
  - Biologically not reasonable.
  - In vivo experiments: $\alpha \ll 1$.

  (Peng et al. 2002, 2006)
- 1/3 virus deactivation per day.
  - Suggested by in vitro experiments

  (Whistler et al., 1996)
  - Consistent fit: $\alpha = 0.9$, $\omega = 0.3$.



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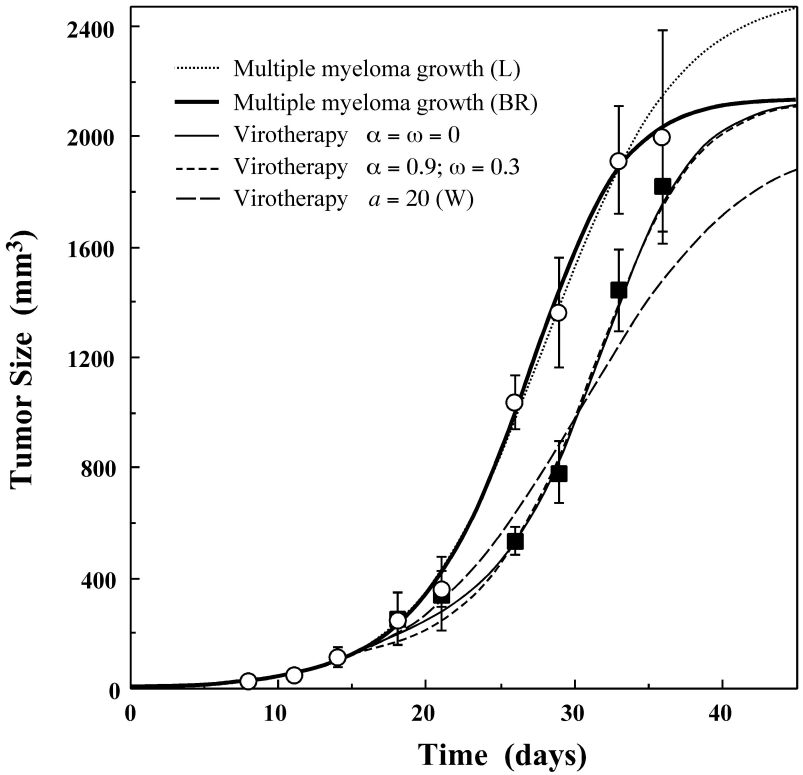
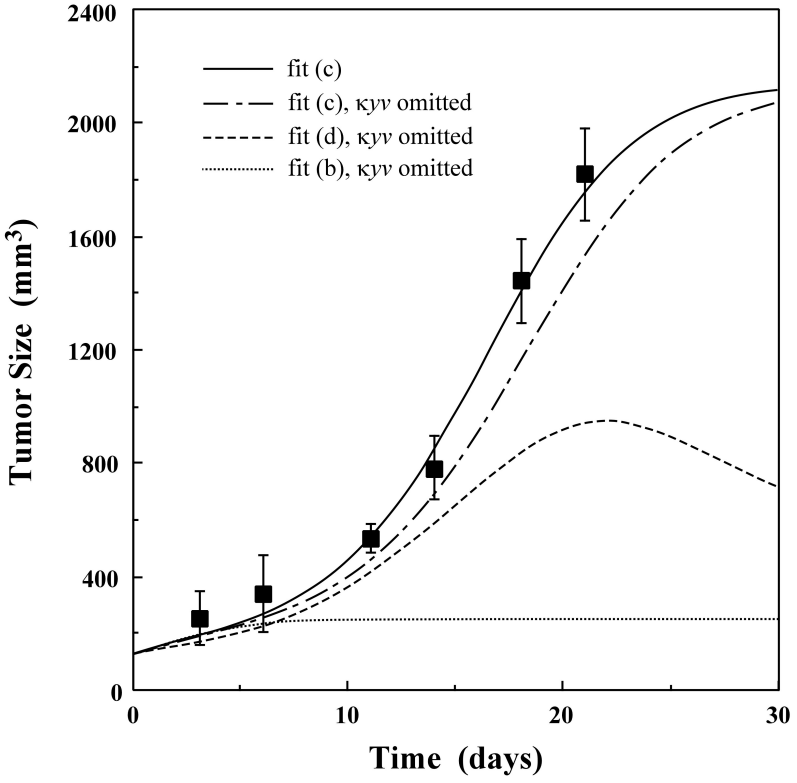


Virion reduction

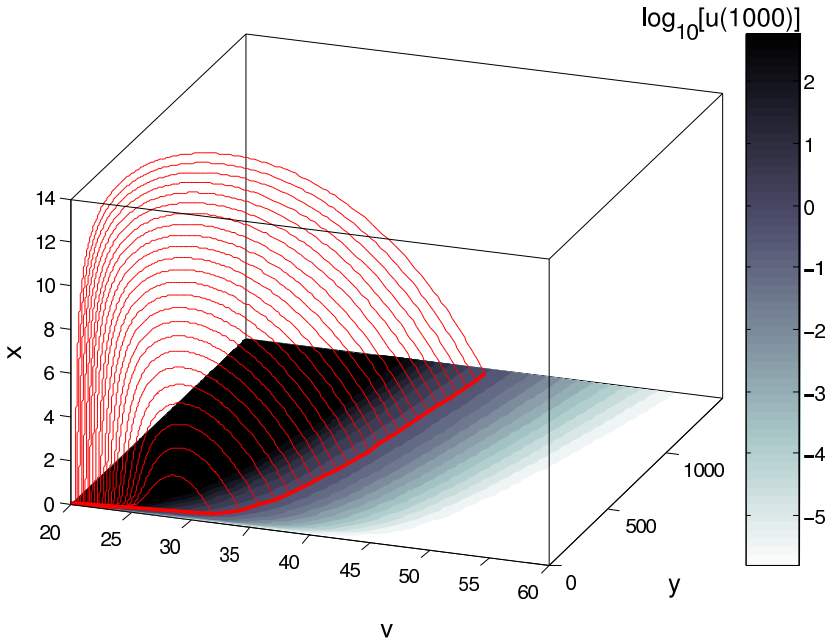
$$\frac{dv}{dt} \sim -\kappa y v$$

Important for proper fit.



Initial tumor vs. virus

- Black: $u(1000) \geq 1$
  Unsuccessful
- Red: $u(1000) = 1$
  Minimum v_0 for success.
- White: $u(1000) \ll 1$
  Success
- Success requires large v_0



Successful therapy

- Search for “reasonable" parameter values that lead to successful therapy.
- Genetically modify the virus to alter growth kinetics or cytopathic effects.

set	κ	δ	α	ω	ρ	$u(1000)$	t_e
$b.1$	0.0009575	0.015	0.053	0.001	0.5	0.99	
$b.2$	0.0009575	0.015	0.25	0.001	0.5	0	952.8
$d.1$	0.0005911	0.021	1.3	0.3	0.1411	1.00	
$d.2$	0.0005911	0.021	1.4	0.3	0.1411	0	758

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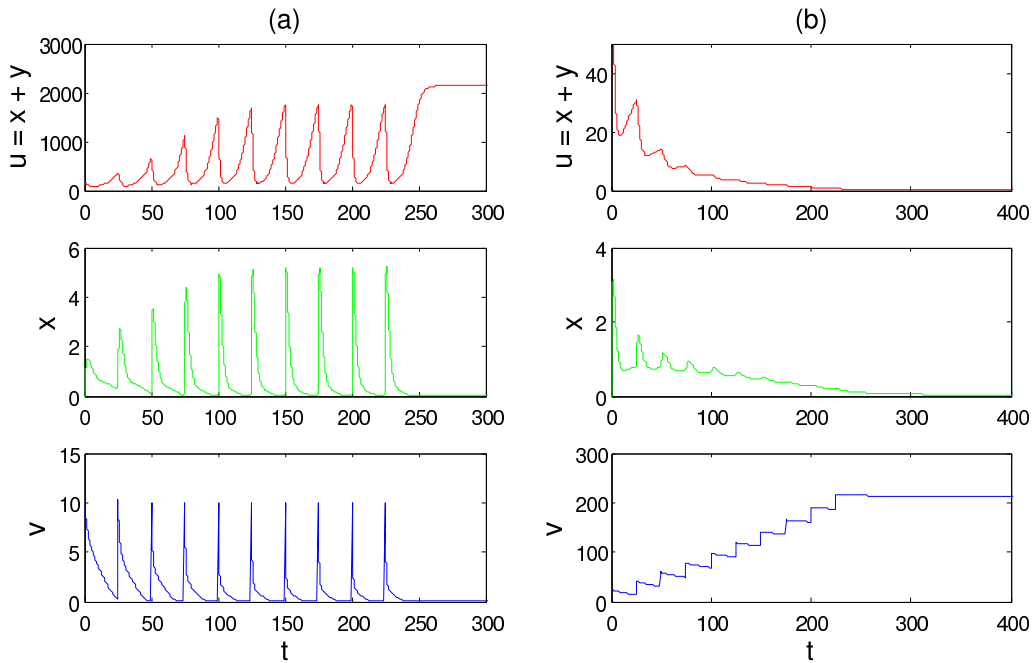
Dose scheduling



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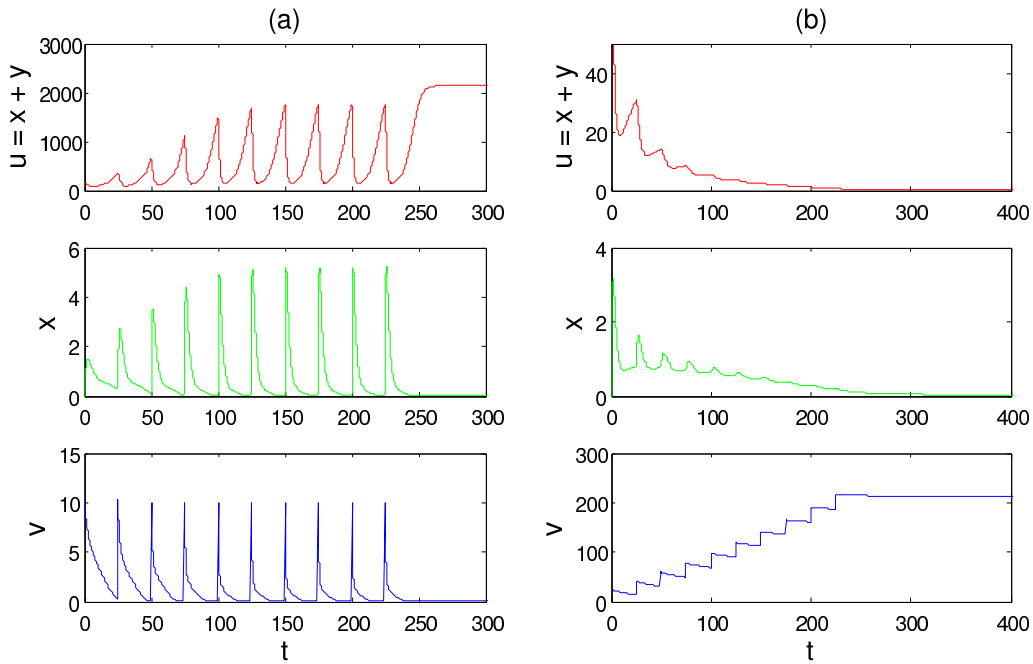

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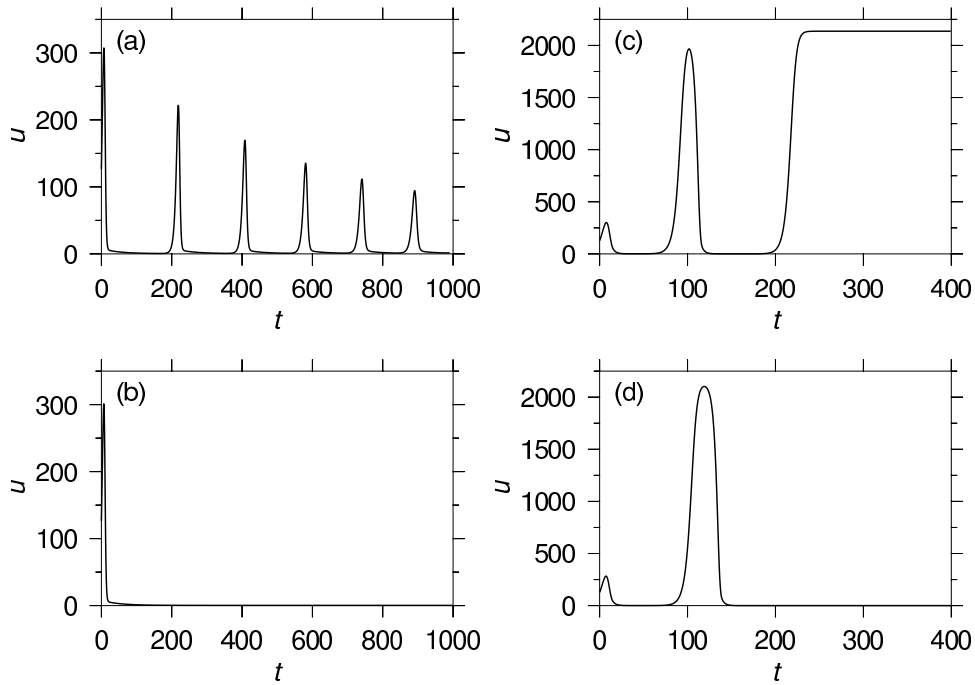

- Between pulses the tumor is very small.
  - May be effectively eradicated.
  - May be undetectable.
- Undetectable $\Rightarrow$ mistaken for success.
- May allow for success use of additional therapies.

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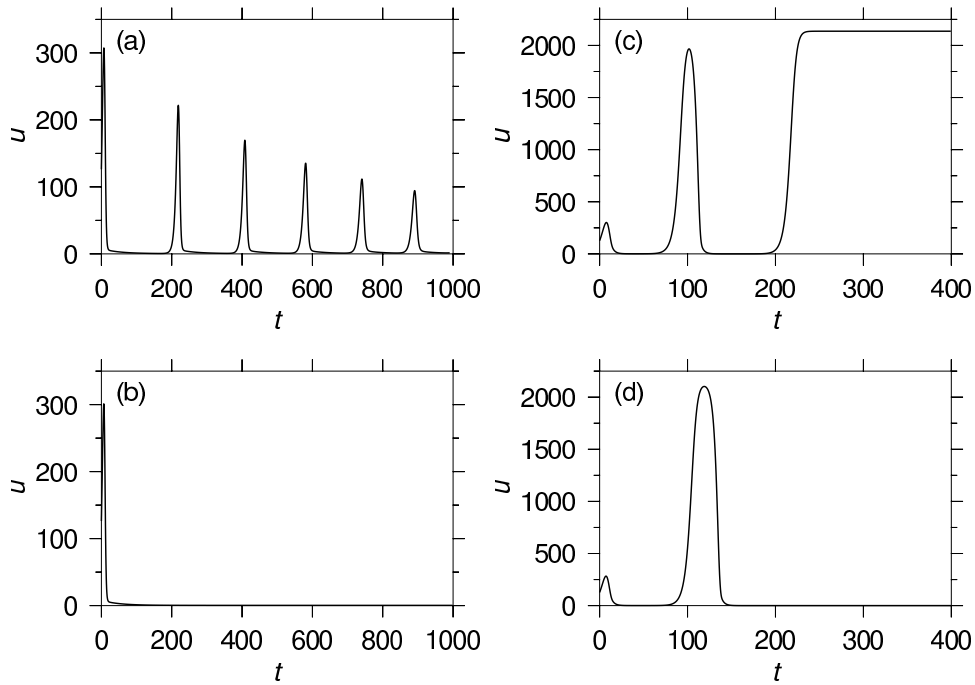

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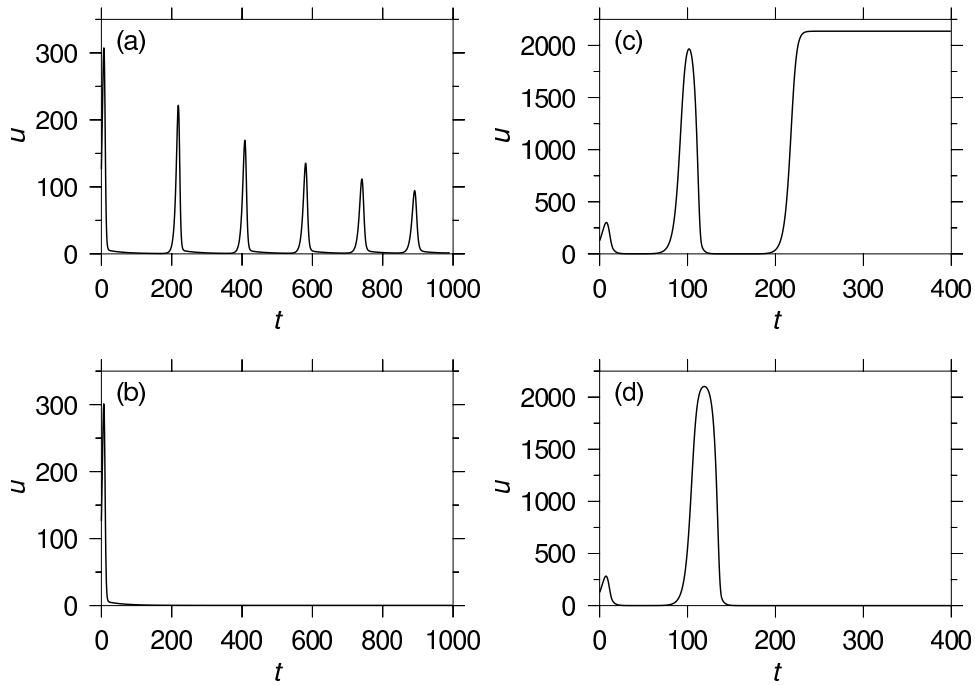

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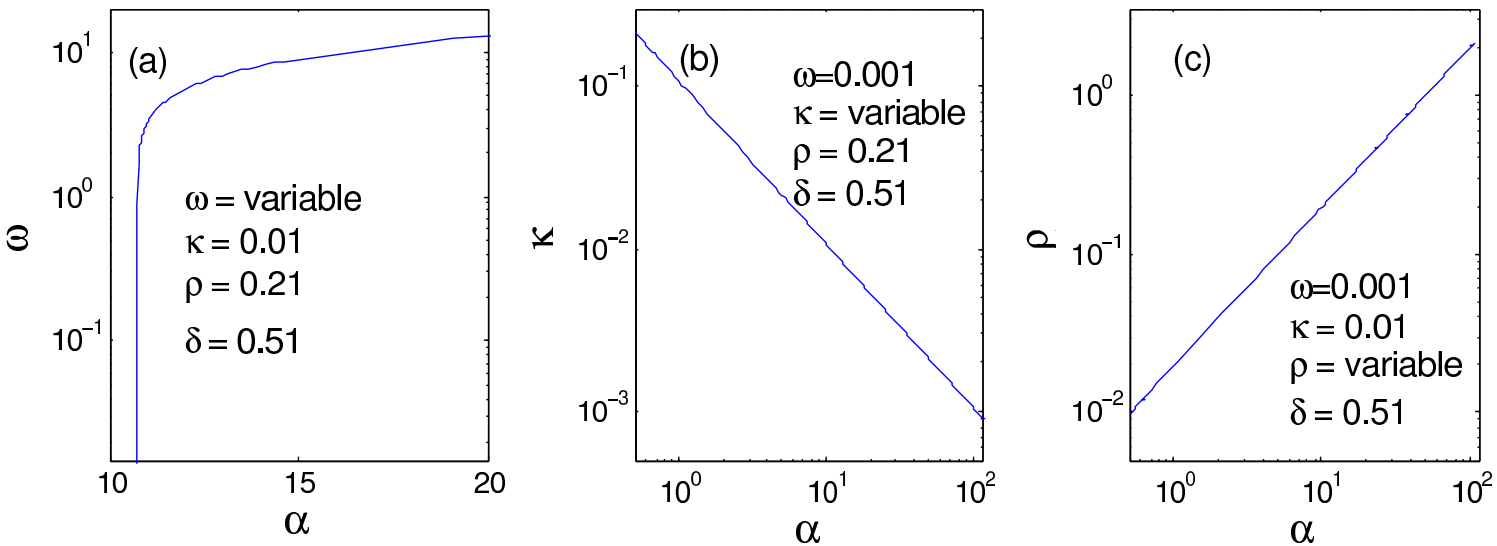
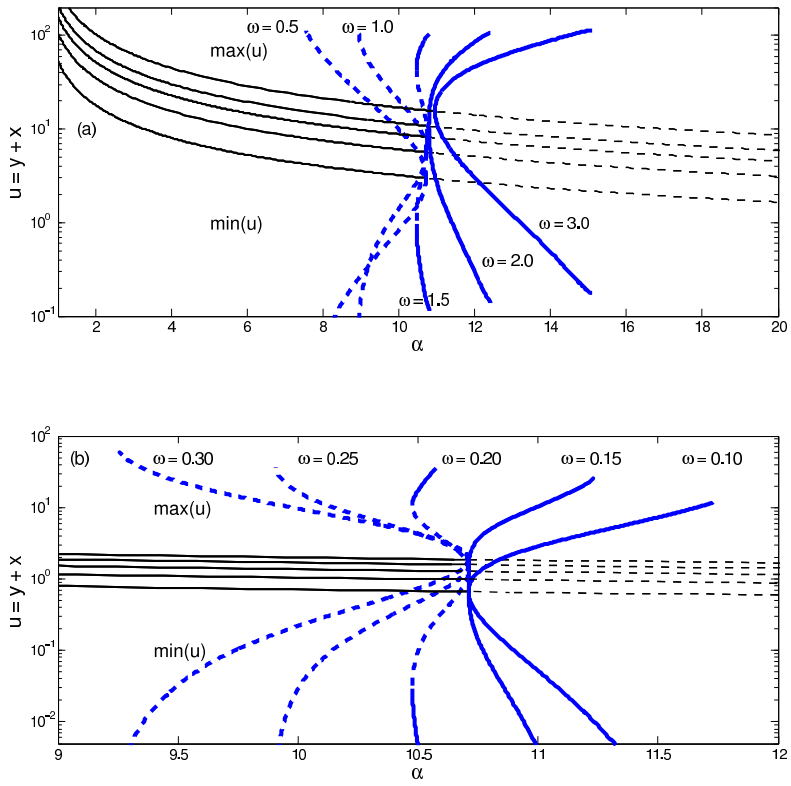
Neutral Stability Curves

Parameter values that support oscillations:



Bifurcation diagrams



Summary

- Virotherapy
  - Viruses evolution rate $\gg$ tumor evolution.
    Avoid therapy resistance.
  - Highly nonlinear and sensitive to ICs.
    Therapy variability in patients.
- Modeling + experimental data.
  - Model captures cell-to-cell fusion (ρ).
    Fusion $\gg$ lysis.
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Summary (cont.)

- Predictions
  - Virus needs help.
    Required initial dose is unrealistically large.
    Dosing schedule not effective.
  - Weak cytopathic viruses (small δ) are more effective.
  - "Larger" alpha induces oscillations.
    May cause diagnostic errors.
    May allow for success via additional therapies.
  - Virotherapy + slow down of tumor growth (+oscillations) most promising.

Summary (cont.)

- New data $\rightarrow$ model improvements.
  - Gompertz logarithmic saturation: $y' = r \ln(K/u)$.
  - Better accounting of syncytia formation s.

  Contact between y and x leads to
  .... new x with probability λ
  ... new s synctia with probability $1 - \lambda$.
  Total volume of tumor is $y + x + x$.

$$
\begin{aligned}
\frac{dy}{dt} &= r \ln\left[\frac{K}{y+x+s}\right] - \kappa y v - \rho x y \\
\frac{dx}{dt} &= \kappa y v - \delta x + \lambda \rho x y \\
\frac{dv}{dt} &= \alpha(x+s) - \omega v - \kappa y v \\
\frac{ds}{dt} &= (1-\lambda)\rho x y - \delta s
\end{aligned}
$$

Details...

- Z. Bajzer, T.W. Carr, D. Dingli and K. Josic, ”Optimization of tumor virotherapy with recombinant measles viruses,” in Optimization in Medicine and Biology, editors: Gino J. Lim and Eva K Lee, (Taylor and Francis, 2007).
- Z. Bajzer, T.W. Carr, K. Josic, S.J. Russel and D. Dingli, “Modeling of cancer virotherapy with recombinant measles viruses,” J. Theoretical Biology 252:109-122, 2008.
- David Dingli, Chetan Offord, Rae Myers, Kah-Whye Peng, Thomas W. Carr, Kresimir Josic, Stephen J. Russell, and Zeljko Bajzer, “Dynamics of multiple myeloma tumor therapy with a recombinant measles virus,” Cancer Gene Therapy, accepted, 2009.