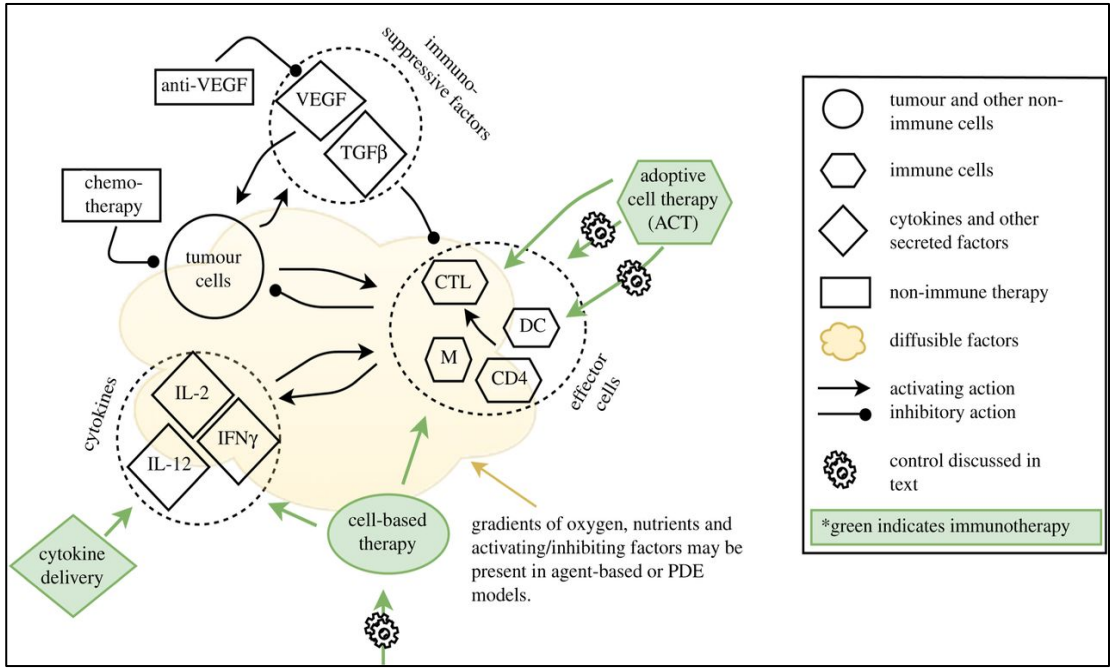
Mathematical models for cancer immunotherapy: a review and new directions



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Department of Immunology, UConn Health

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Adam Adler, Professor

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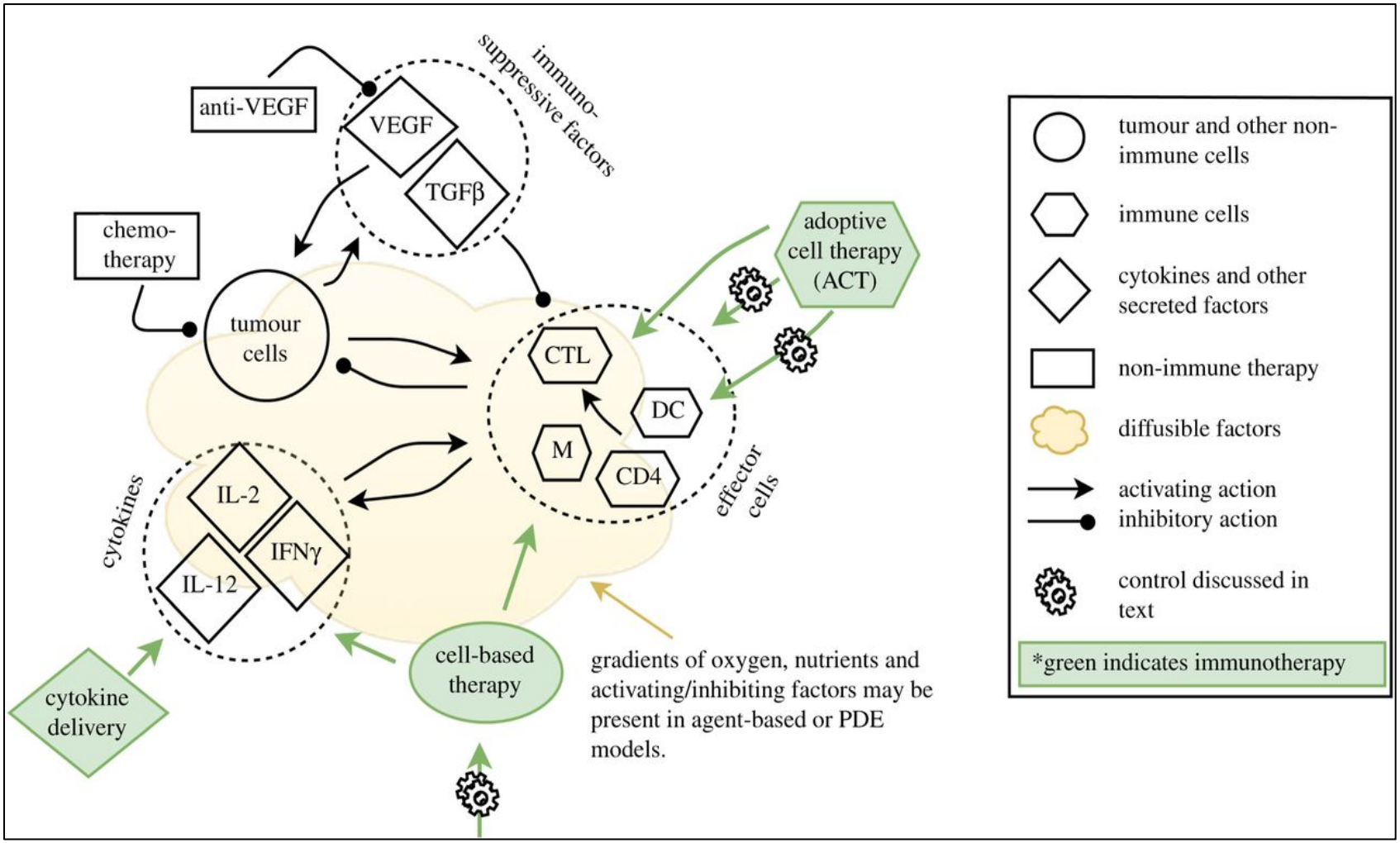
Overview

I. Mathematical models for immunotherapy: current progress and challenges[1]
   i. Tumor classification for treatment and prediction of response
   ii. Optimal scheduling and dosage of treatment
   iii. Design and identification of combination treatment regimes
   iv. Recommendations for further progress

II. A mathematical model of combined CD8 T cell costimulation by 4-1BB (CD134) and OX40 (CD137) receptors[2]

[1]Konstorum A, Vella AT, Adler AJ, Laubenbacher RC (2017) Addressing current challenges in cancer immunotherapy with mathematical and computational modelling. *J. R. Soc. Interface* 14: 20170150.
[2]Currently manuscript in preparation, results not (yet!) published. Stay tuned!

Summary of modeling efforts in immunotherapy



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Challenge: tumor classification for treatment and prediction of response

- Goal: to predict how a patient with a specific set of tumor characteristics will respond to a given treatment.
- Mathematical models can be used to predict effect of therapy that has not yet been tried in the clinic.

Classic example: Panetta-Kirschner (PK) model[1]

- Models dynamics of effector (*E*) and tumor (*T*) cells, and the cytokine IL-2 (I_L).
- Parameter of note:
  - antigenecity of tumor (c)
- Therapies represented by s_1, s_2.
  - s_1:= Adoptive Cellular Immunotherapy (ACI), injection of cultured immune cells with anti-tumor reactivity or Tumor Infiltrating Lymphocyte (TIL) therapy: tumor-derived lymphoyctes cultured and reinjected into patient.
  - s_2:= external input of IL-2 into the system.

$$\frac{dE}{dt} = cT - \mu_2 E + \frac{p_1 E I_L}{g_1 + I_L} + s_1,$$
$$\frac{dT}{dt} = r_2(T)T - \frac{aET}{g_2 + T},$$
$$\frac{dI_l}{dt} = \frac{p_2 ET}{g_3 + T} - \mu_3 I_L + s_2,$$

with initial conditions

$$E(0) = E_0, \quad T(0) = T_0, \quad I_L(0) = I_{L_0}$$

[1]Kirschner, D and Panetta, JC (1998) Modeling immunotherapy of the tumor – immune interaction. *J. Math Biol* 37:235-252.

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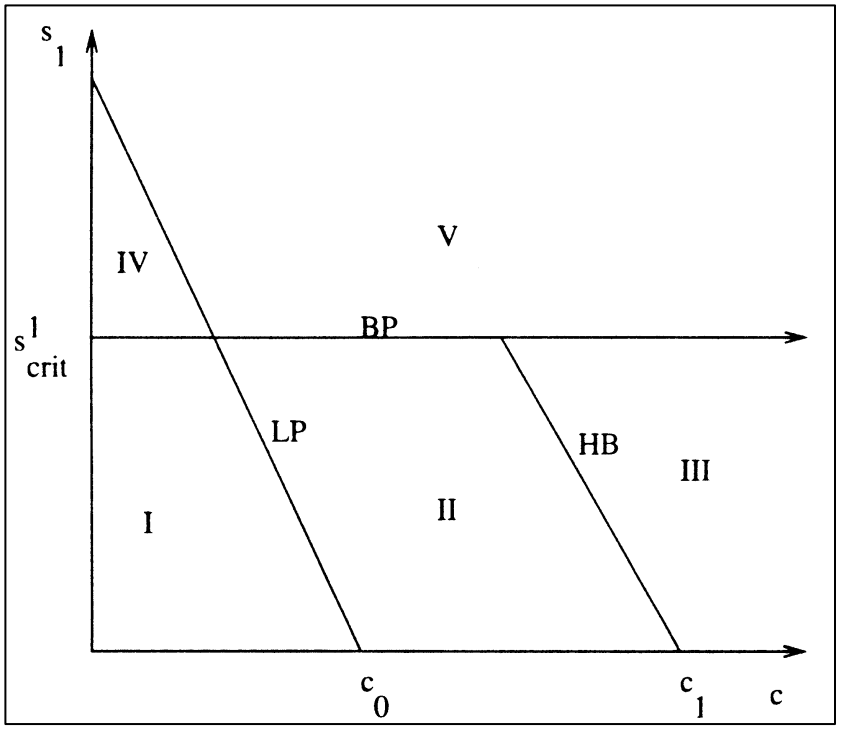
- Using linear stability analysis, identify

$$s^1_{\text{crit}} = \frac{r_2 g_2 \mu_2}{a}$$

which impacts the tumor steady state.

- Region V has a stable steady state of tumor eradication, and Region IV may either tend to tumor eradication or survival depending on the initial conditions.
- Regions I-III do not produce tumor eradication.

Therefore, can predict response to (and potentially modify) treatment with knowledge of system parameters.



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Challenge: tumor classification for treatment and prediction of response

- More complex systems require numerical analysis (vs. linear stability), and have focused on the concept of thresholds for predicting patient response. Some examples:
  - Kronik et al. (2012)[1] modeled *ex vivo* expanded tumor-specific T cell transfer for melanoma using a system of ODEs and used clinical data for retroactive validation.
    - Varied initial tumor size and growth rate to imitate a virtual population. Four different therapy regimens were simulated to correspond to four different clinical trials. Identified a tumor-size threshold for therapy effectiveness which matched patient data.
  - Wells et al (2015)[2] developed a hybrid discrete-continuous (HDC) agent-based model (ABM). These models treat cells as agents that can interact with and respond to other cells.
    - Observed that the ratio of M2 macrophages to other cell types was predictive of tumor survival. Spatial model necessary for predictive capability.
  - Eikenberry et al (2009)[3] developed a PDE of melanoma with immune infiltrate.
    - Showed that surgical removal of tumors with high levels of immune infiltrate could promote growth of satellite metastases, as was observed clinically.
    - Hence, provided a model-based hypothesis for tumor classification with respect to responsiveness to surgery.

[1]Kronik et al. (2012) Improving T-cell immunotherapy for melanoma through a mathematically motivated strategy: efficacy in numbers? *J. Immunother.* 35, 116-124.

[2]Wells et al. (2015) Spatial and functional heterogeneities shape collective behavior of tumor-immune networks. *PLoS Comput. Biol*. 11, e1004181.

[3]Eikenberry et al. (2009) Tumor-immune interaction, surgical treatment, and cancer recurrence in a mathematical model of melanoma. *PLoS* Comput. Biol. 5, e1000362.

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Challenge: optimal scheduling and dosage of treatment

- If you know the treatment – how to determine the optimal schedule and dosage (not based on trial and error)?
- Techniques to identify optimal treatment schedules *in silico* include:

Optimal control theory[1]

- Used for models based on continuum methods.
- States the problems of finding an optimal treatment plan in the framework of a controlled dynamical system.
- Example: identify optimal ACI therapy in PK model to minimize final tumor concentration[2]

Genetic Algorithms[3]

- Belong to class of evolutionary algorithms.
- System can be agent-based, discrete, continuous, etc.
- Theory based on principles of genetic evolutionary theory.
- Example: identify optimal vaccine schedule for the Triplex vaccine (for HER-2/neu-positive BC) using an agent-based SimTriplex Model[4]

[1]Evans LC (2017). An introduction to mathematical optimal control theory, Version 0.2. See https://math.berkeley.edu/evans/control.course.pdf
[2]Burden et al (2004). Optimal control applied to immunotherapy. *Discr. Continuous Dyn. Syst. Series B* 4, 135-136.
[3]Whitley D. (1994). A genetic algorithm tutorial. *Stat. Comput.* 4, 65-85
[4]Lollini et al. (2006). Discovery of cancer vaccination protocols with a genetic algorithm driving an agent based simulator. *BMC Bioinform.* 7, 352.

Challenge: design and identification of combination treatment regimes

- Mathematical modeling can help in rational design of combination immunotherapy (either with just immunotherapeutic agents or with immune- and non-immunotherapeutic agents) to maximize treatment response.

Example 1: de Pillis et al. (2009)[1]: chemo-immunotherapy model.

- Model comprised of six ODEs for combination chemo- and immunotherapy that includes tumor and immune cells, and concentrations of chemo- and immuno-therapy drugs.
- Found that success of combination versus monotherapy different based on initial patient characteristics (derived from human clinical trials of metastatic melanoma).

Simulation	$T = 1 \times 10^6$ cells		$T = 1 \times 10^7$ cells		$T = 1 \times 10^8$ cells		$T = 1 \times 10^9$ cells	
Patient number	9	10	9	10	9	10	9	10
No treatment	*x*	*x*	*o*	*o*	*o*	*o*	*o*	*o*
Chemotherapy	*x*	*x*	*x*	*x*	*x*	*x*	*o*	*o*
Immunotherapy	*x*	*x*	*x*	*o*	*o*	*o*	*o*	*o*
Chemo-immuno	*x*	*x*	*x*	*x*	*x*	*o*	*o*	*o*

[1]de Pillis et al. (2006) Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretatiosn. *J. Theor. Biol.* 238: 841-862.

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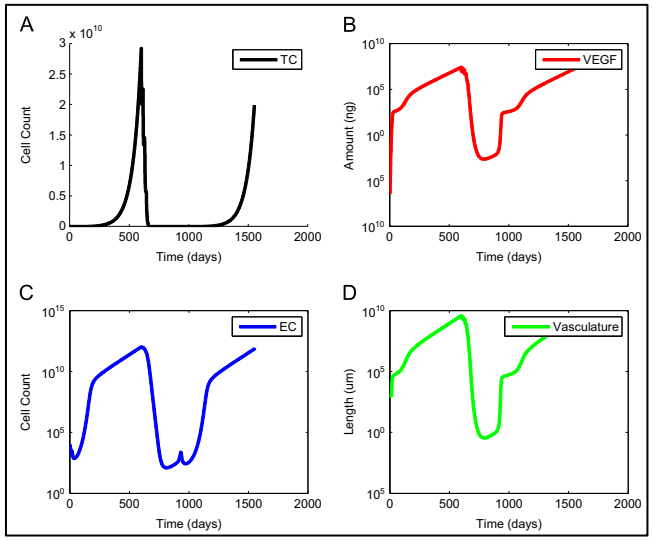
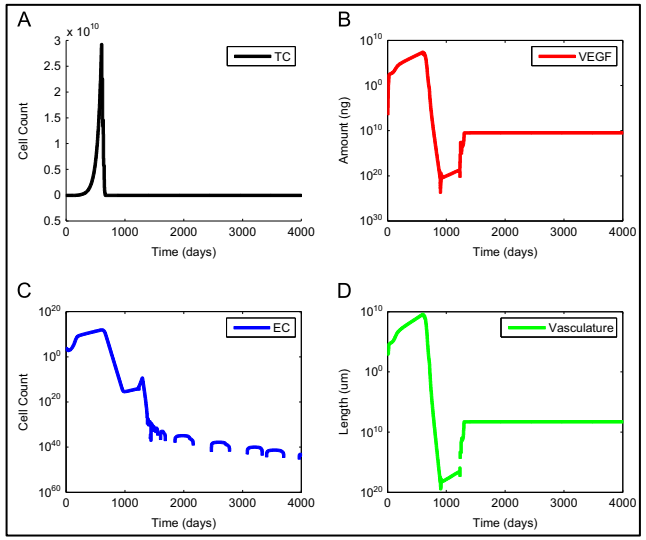
Example 2: Soto-Ortiz et al. (2016)[1]: anti-angiogenic and immunotherapy model

- Model comprised of 18 ODEs that include tumor, immune and vascular endothelial cells, and several cytokines and growth factors modeling anti-VEGF therapy (VEGF has pro-angiogenic and immunosuppressive activity) and administration of DC cells.

Anti-VEGF alone



Anti-VEGF + DC



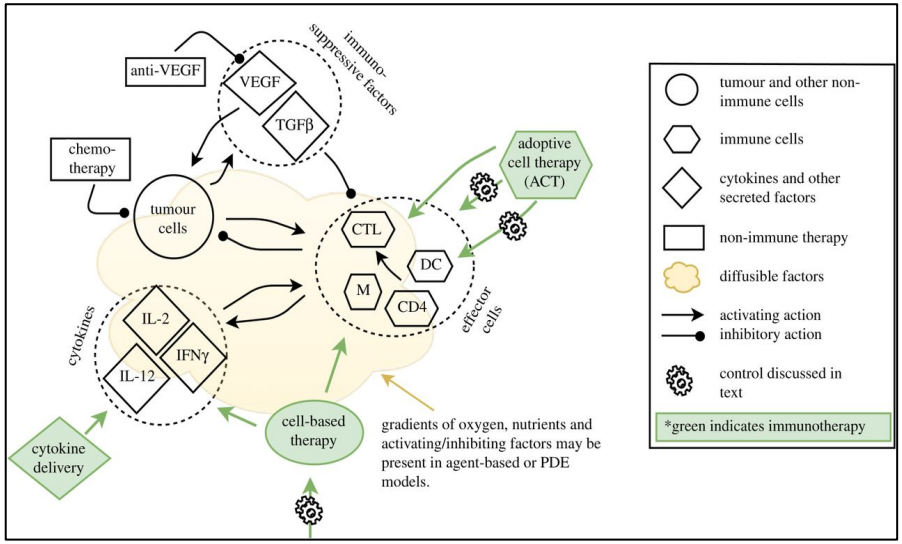
[1]Soto-Ortiz and Finley et al. (2016) A cancer treatment based on synergy between anti-angiogenic and immune cell therapies. *J. Theor. Biol.* 394: 197-211.

Recommendations

I. Intracellular and multi-scale modeling
   i. Can give insights into therapeutic action at intracellular level, and relative contribution of cell-cell and intracellular activities.
   ii. Can be developed from existing models of signaling cascades in cancers.

II. Addressing toxicity
   i. Incorporation of immunotherapy-related toxicity can help to optimize therapy predictions for maximum efficacy/minimum toxicity.

III. Experimental and clinical validation of immunotherapy models.
   i. Main bottleneck for wider validation and use of mathematical and computational models for purpose of developing novel therapies.
   ii. Needs to be community-level initiative (at scale of organization or funding agencies).



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Recommendations

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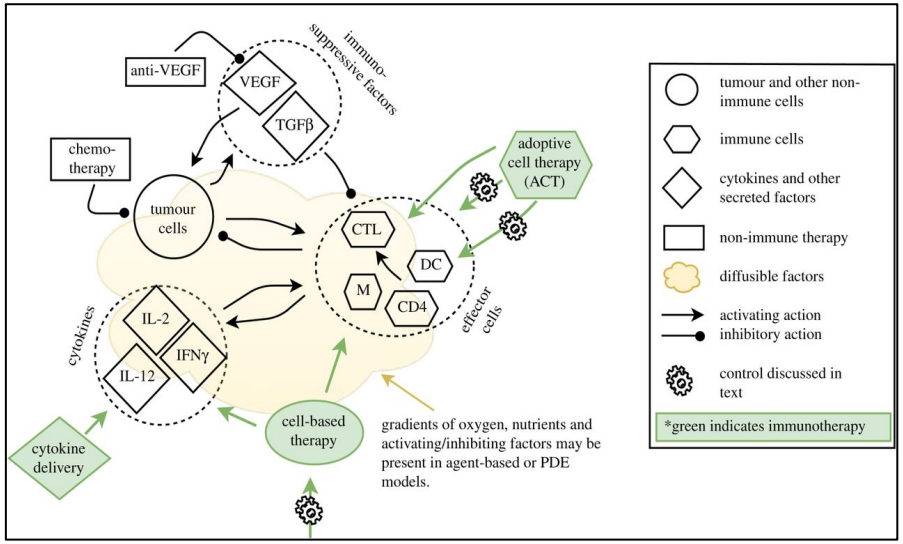

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