SITC 2017

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NATIONAL HARBOR MARYLAND

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Society for Immunotherapy of Cancer

Presenter Disclosure Information

Doron Levy

The following relationships exist related to this presentation:

No Relationships to Disclose

Mathematics and Immunotherapy

- CML – Cancer Vaccines
- CML – Signature of the (Individual) Immune Response
- Solid Tumors
- Complexity

Dynamics and Potential Impact of the Immune Response to Chronic Myelogenous Leukemia

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Abstract

Recent mathematical models have been developed to study the dynamics of chronic myelogenous leukemia (CML) under imatinib treatment. None of these models incorporates the anti-leukemia immune response. Recent experimental data show that imatinib treatment may promote the development of anti-leukemia immune responses as patients enter remission. Using these experimental data we develop a mathematical model to gain insights into the dynamics and potential impact of the resulting anti-leukemia immune response on CML. We model the immune response using a system of delay differential equations, where the delay term accounts for the duration of cell division. The mathematical model suggests that anti-leukemia T cell responses may play a critical role in maintaining CML patients in remission under imatinib therapy. Furthermore, it proposes a novel concept of an "optimal load zone" for leukemic cells in which the anti-leukemia immune response is most effective. Imatinib therapy may drive leukemic cell populations to enter and fall below this optimal load zone too rapidly to sustain the anti-leukemia T cell response. As a potential therapeutic strategy, the model shows that vaccination approaches in combination with imatinib therapy may optimally sustain the anti-leukemia T cell
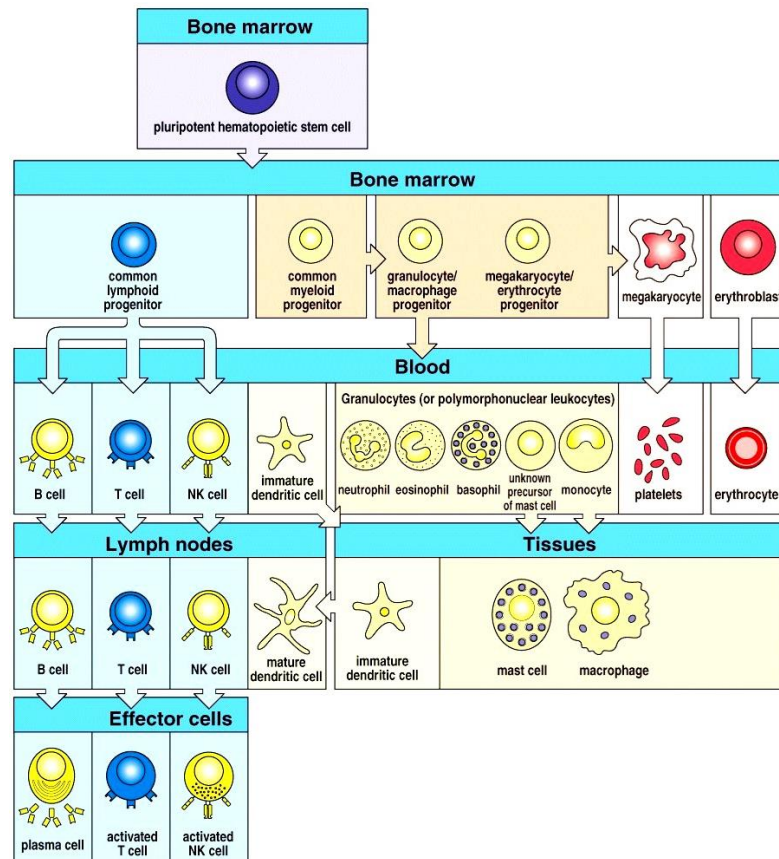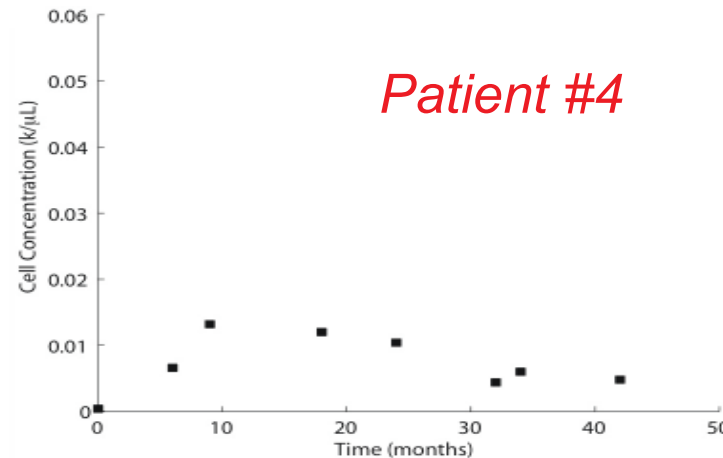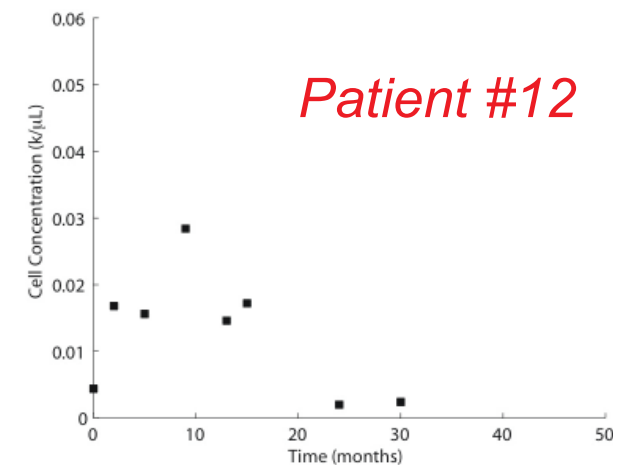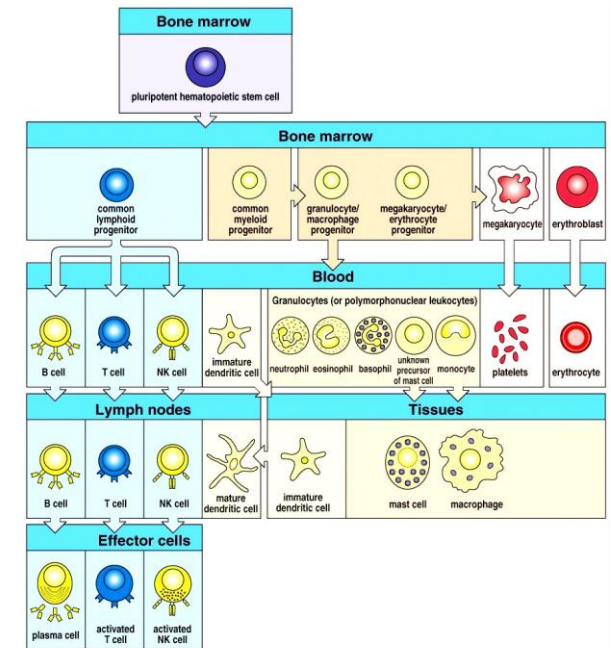
Complex Dynamics: CML, TKI, Immune system

Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

Patient #4

Patient #12

50 Months

50 Months

- Chen *et al.* (Blood, 2008)

Complex Dynamics: CML, TKI, Immune system

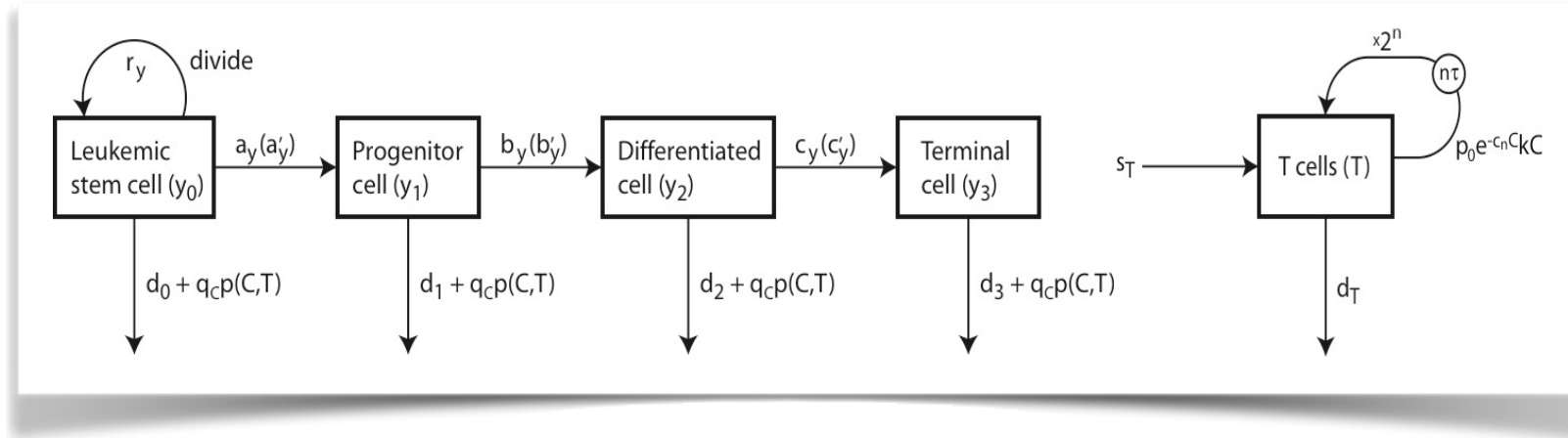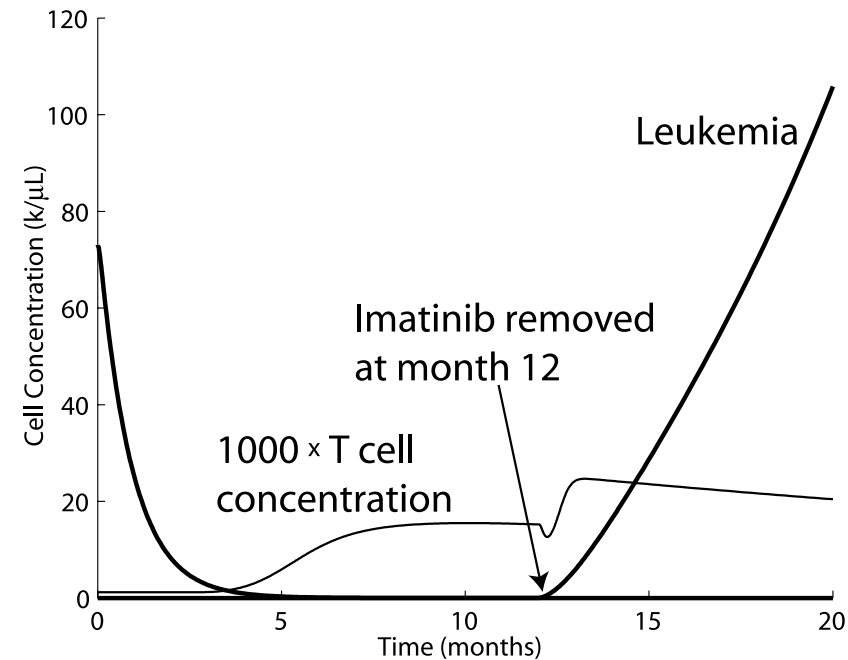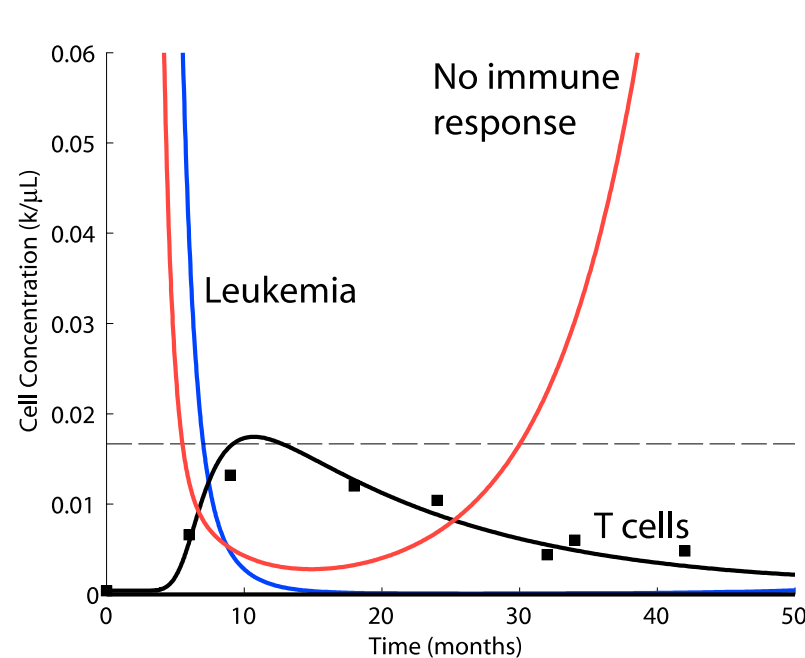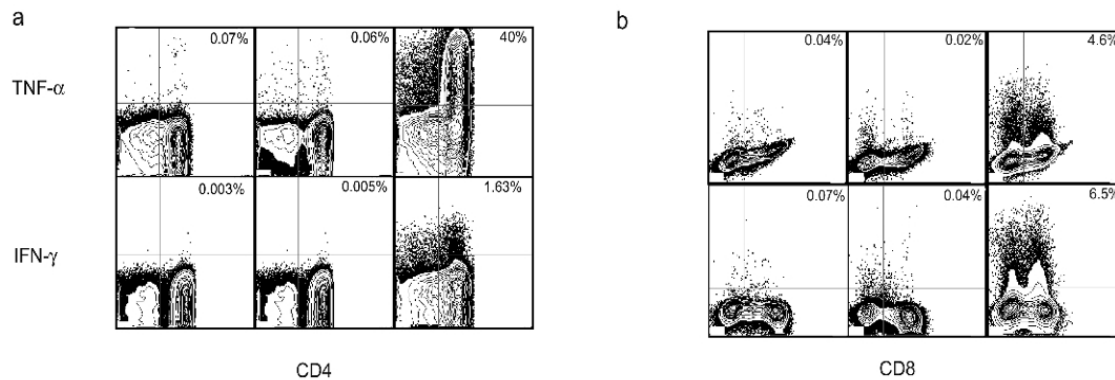- Converting the flowchart into a mathematical model

Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

Simulations of the Mathematical Model

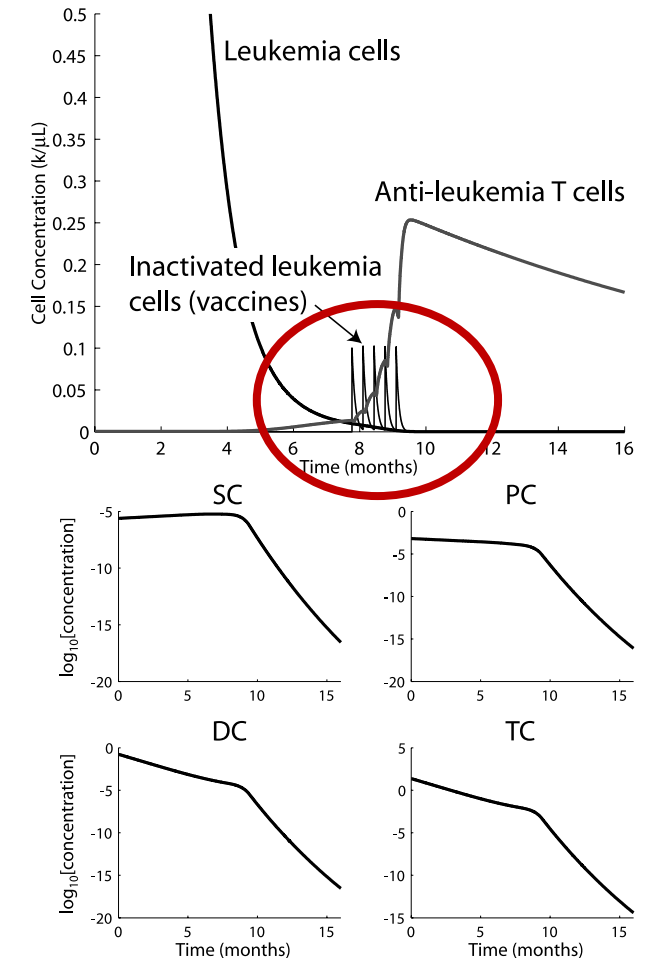• Red = Michor *et al. (Nature '05).* Blue = Kim *et al. (PLoS Comp Bio '08)*
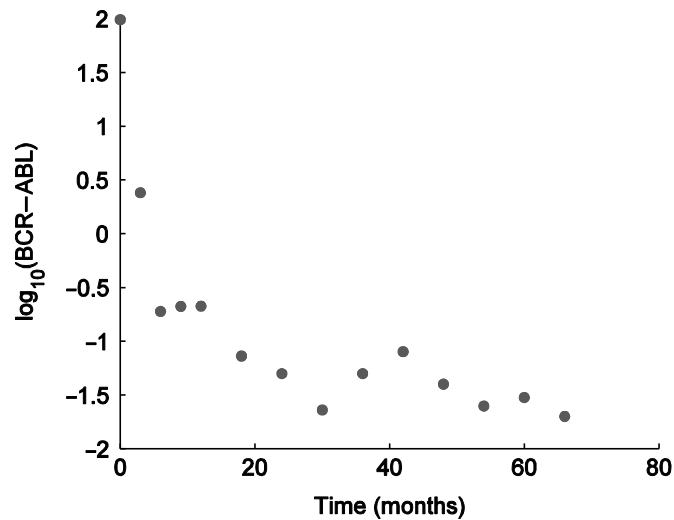
Stimulating the Immune Response

- Mathematical Model
- Dosage + Timing (!)
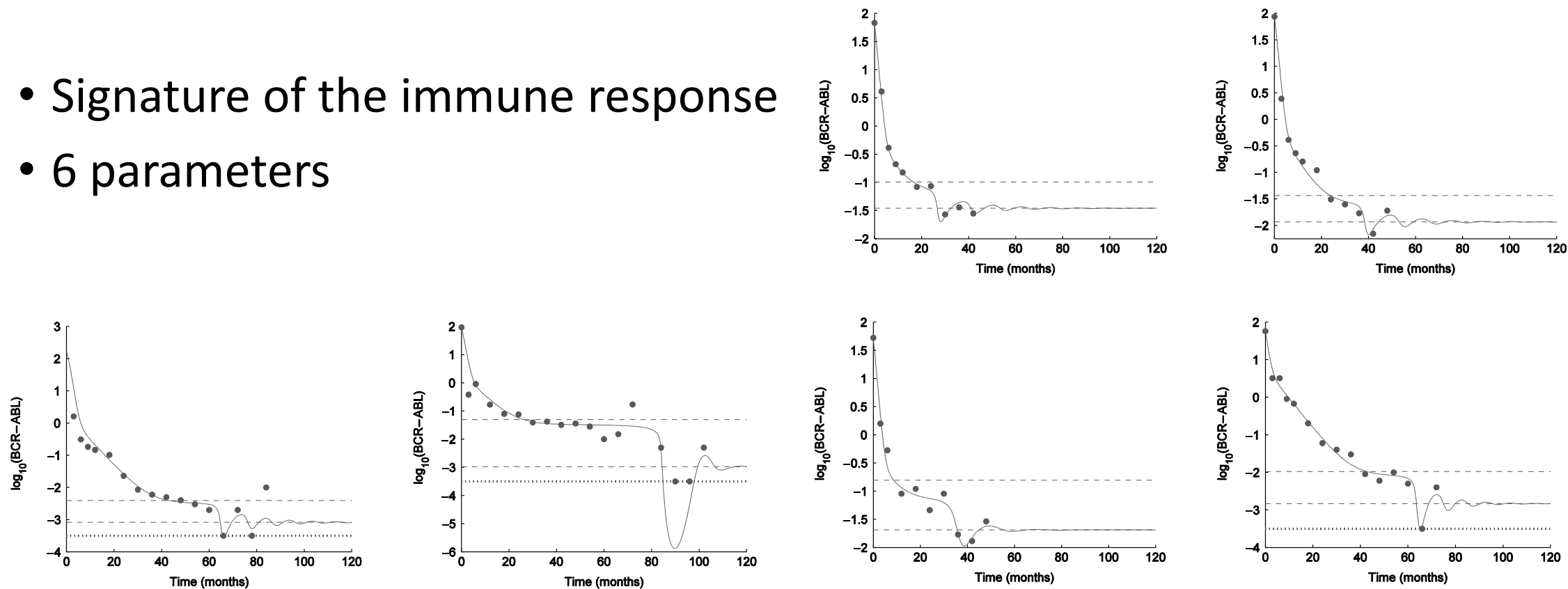- Adjusted to each patient

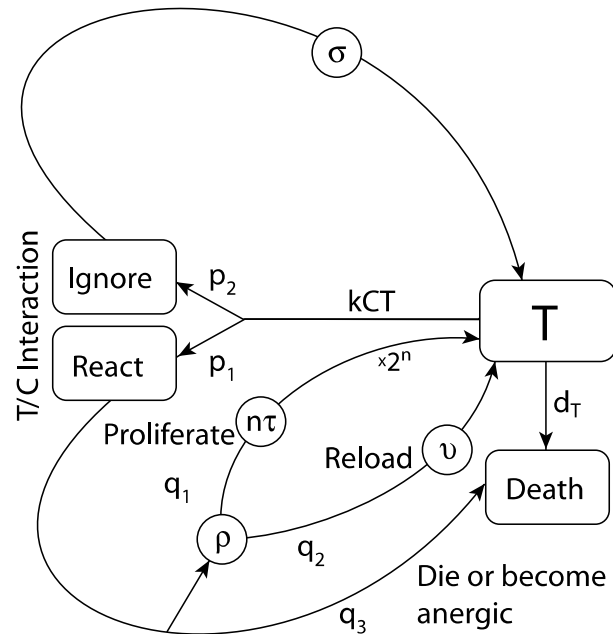# Clapp *et al., Cancer Research 2015*

- CML Patients (Nicolini, Lyon)

Modeling immune system dynamics

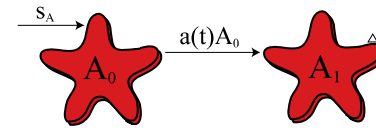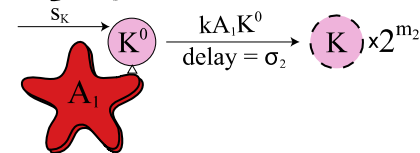- Signature of the immune response
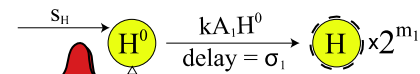- 6 parameters

Complexity of models

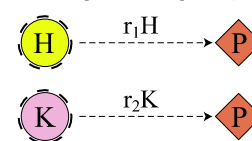- Niculescu *et al.* (DCDS, 2008)
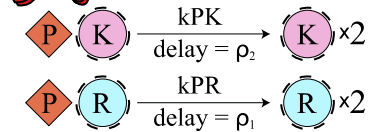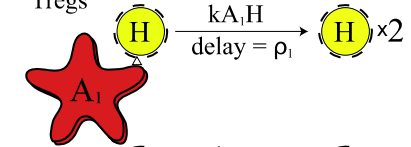

1) Migration of APCs to lymph node
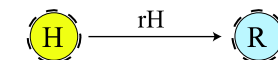
2) Initial T cell activation

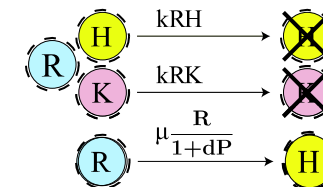3) CD4+ and CD8+ T cells secrete positive growth signal (IL-2)

4) APC-driven proliferation of CD4+ cells. IL-2-driven proliferation of CD8+ cells & Tregs

5) CD4+ T cells differentiate into Tregs

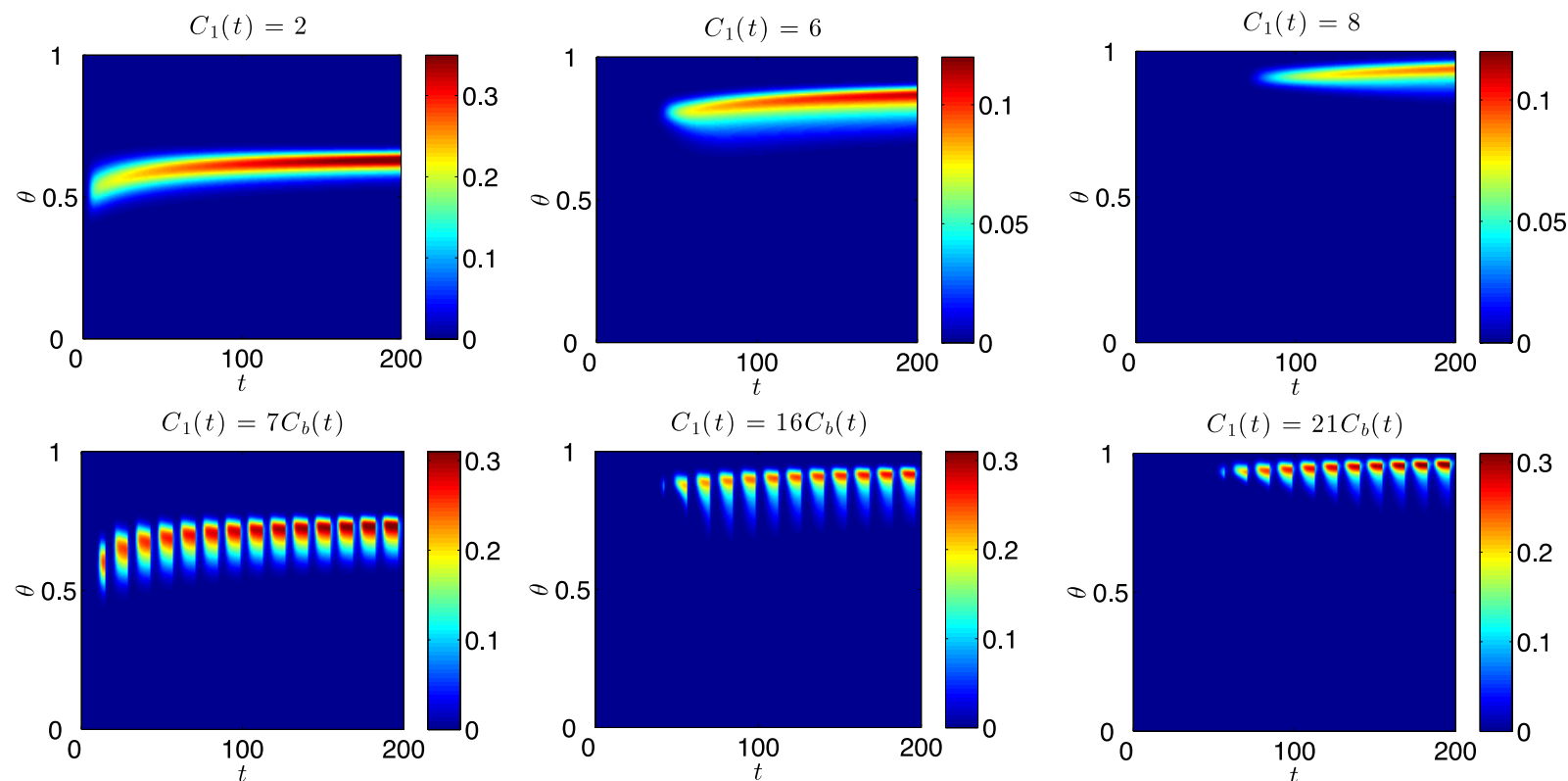6) Tregs suppress effector T cells, and transition into helper T cells.

- Wilson & Levy (BMB, 2013)

Heterogeneity of solid tumors

- Cho & Levy

  (BMB & JTB, 2018)

Lessons and Take Home Messages

- Math complements other quantitative approaches
- Interdisciplinary: experiments/clinical/quantitative sciences
- Math can be useful in modeling dynamics
- Quantifying the Timing + Dosage
- Personalized medicine