Johns Hopkins Engineering

Immunoengineering

Immunoengineering: Modeling

Modeling T Cell Killing

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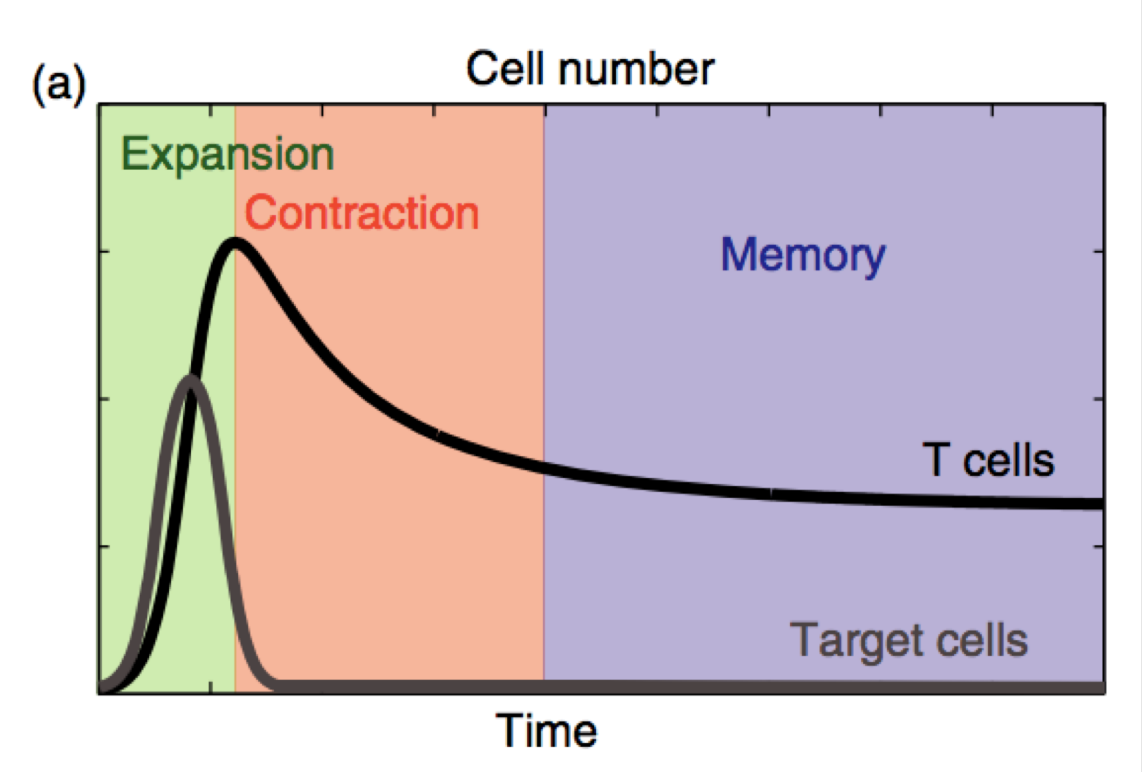
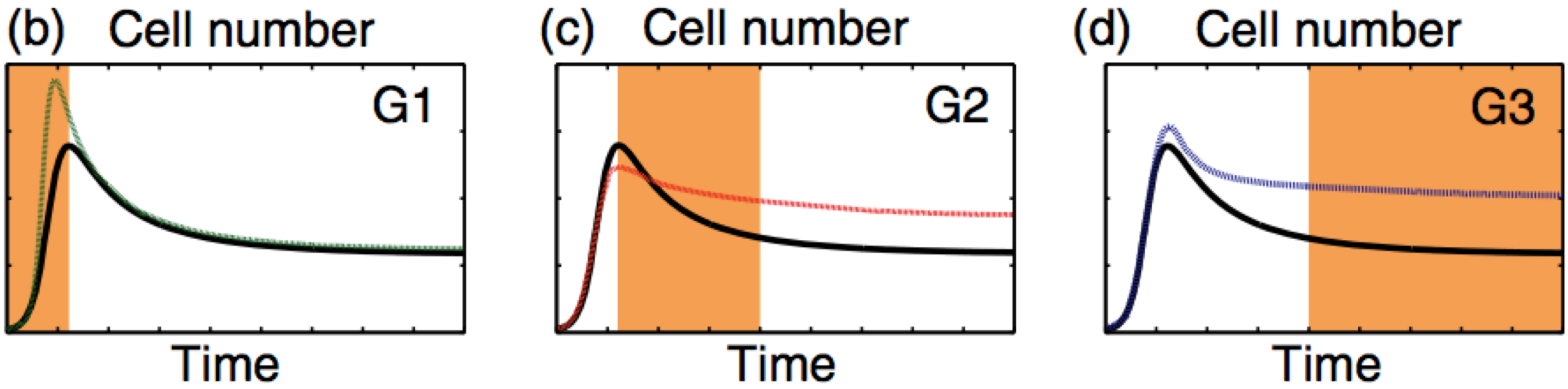
Phases of antigen-specific T cell response



Lorenzi et al. “Mathematical model reveals how regulating the three phases of T-cell response could counteract immune evasion” *Immunology* 146, (2015): 271-280.

Therapeutic Intervention



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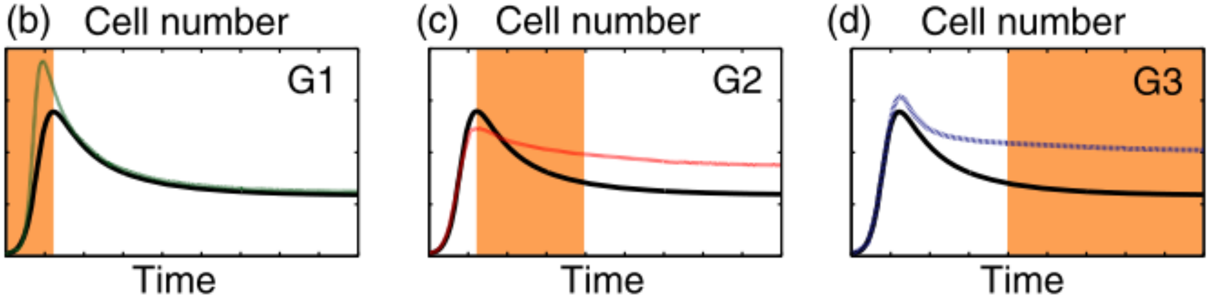
Model to predict targets for immunotherapy

- Predator-prey dynamics

- Introduces 3 hypothetical immunological agents that can alter 3 phases:
  - Increase antigen-driven expansion $c_E(t)$
  - Enhance antigen-independent proliferation $c_P(t)$
  - Promote self-renewal of antigen-specific T cells $c_M(t)$

$c_E(t)>0$ **$c_P(t)>0$** **$c_M(t)>0$**



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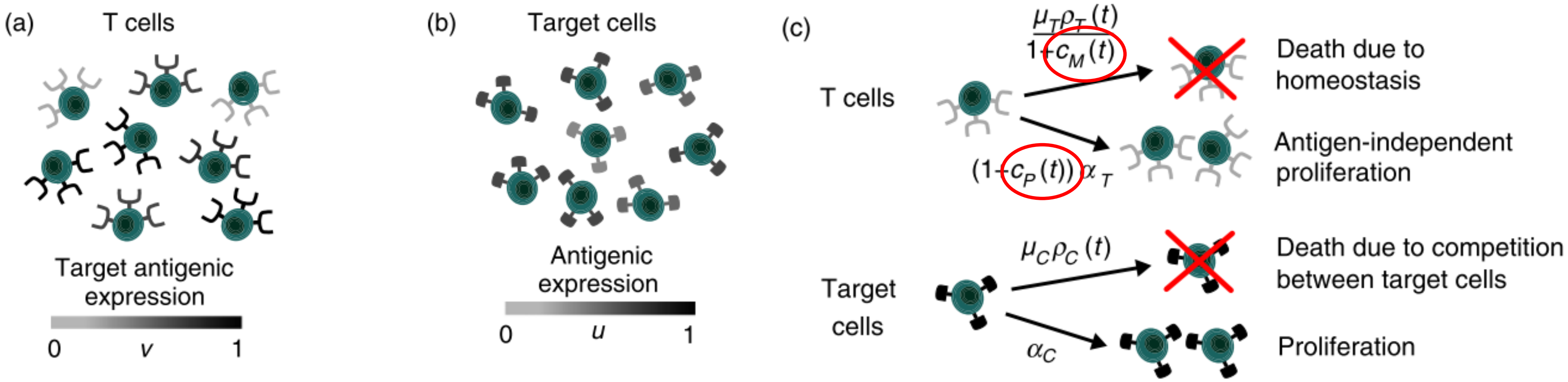
T cell-target cell as predator-prey dynamics



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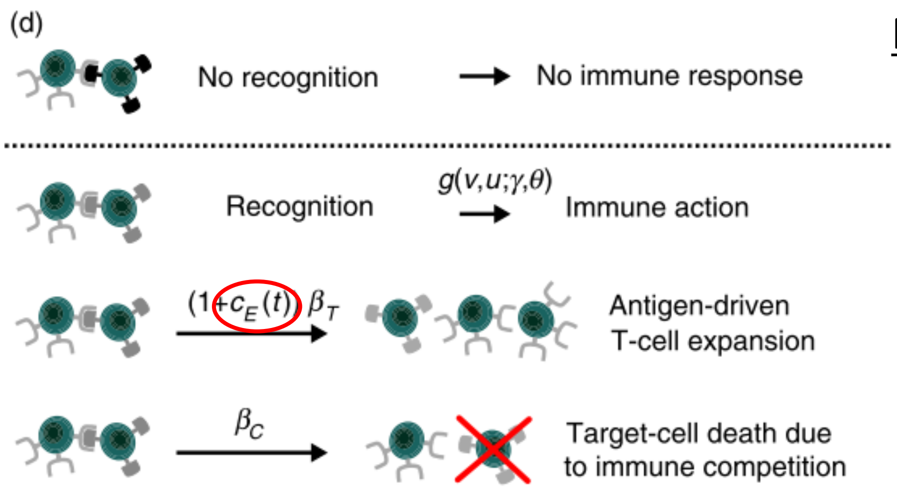

<u>Rate of clonal expansion, target cell death</u>

$$\eta_T(v,u) := \beta_T g(v,u;\gamma,\theta),$$
$$\eta_C(u,v) := \beta_C g(u,v;\gamma,\theta)$$

$\beta_T>0$ – avg killing rate of target cells
$\beta_C>0$ – avg T cell replication rate
$\Theta>0$ – avg affinity range of T cell receptors
$\gamma>0$ – maximum affinity

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Model parameters

Table 1. Values and sources of the parameters in the mathematical model

Parameter	Biological meaning	Value	Source
α_C	Rate of target-cell proliferation	3/day	[12,13,19]
α_T	Rate of antigen-independent T-cell proliferation	5×10^{-2}/day	[20,21]
μ_C	Rate of death due to competition between target cells	$1{\cdot}5 \times 10^{-6}$ µl/day	*ad hoc*
μ_T	Rate of T-cell death due to homeostatic regulation	$2{\cdot}5 \times 10^{-6}$ µl/day	*ad hoc*
β_C	Killing rate of target cells by T cells	1×10^{-5} µl/day	[12,13,19]
β_T	Rate of T-cell replication following recognition	3×10^{-5} µl/day	[12]
θ	Average affinity range of T-cell receptors	$1 \times 10^{-3} \div 1 \times 10^{-1}$	[12,22]
γ	Maximum affinity	$1 \times 10^{-2} \div 3$	[15,19]

The values of the parameters α_C, α_T, β_C and β_T are consistent with previous measurement and estimation studies on the immune response mediated by T cells.[12,13,19–21] The values of the parameters μ_C and μ_T are selected to guarantee that the carrying capacities of the two cell populations are biologically consistent. The range of values of the parameter θ is consistent with experimental estimations of the precursor frequency of T cells,[22] and it is computed through a strategy analogous to that presented in ref. 12. The values of the parameter γ are consistent with those used in refs 15,19.

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Mathematical Model

We describe the selection dynamics in the cell system through the following coupled integro-differential equations:

$$\frac{\partial}{\partial t} n_C(t,u) = \underbrace{[\alpha_C - \mu_C\, \rho_C(t)] n_C(t,u)}_{\text{proliferation and death of target cells}} - \underbrace{n_C(t,u) \int_0^1 \eta_C(u,v) n_T(t,v) dv,}_{\text{selective action exerted by T cells}} \quad (1)$$

$$\frac{\partial}{\partial t} n_T(t,v) = \underbrace{[1 + c_E(t)] n_T(t,v) \int_0^1 \eta_T(v,u) n_C(t,u) du}_{\text{antigen-driven expansion}} + \underbrace{[1 + c_P(t)]\, \alpha_T\, n_T(t,v)}_{\text{antigen-independent proliferation}}$$

$$- \underbrace{\frac{\mu_T}{1 + c_M(t)}\, \rho_T(t)\, n_T(t,v).}_{\text{homeostatic regulation}} \quad (2)$$

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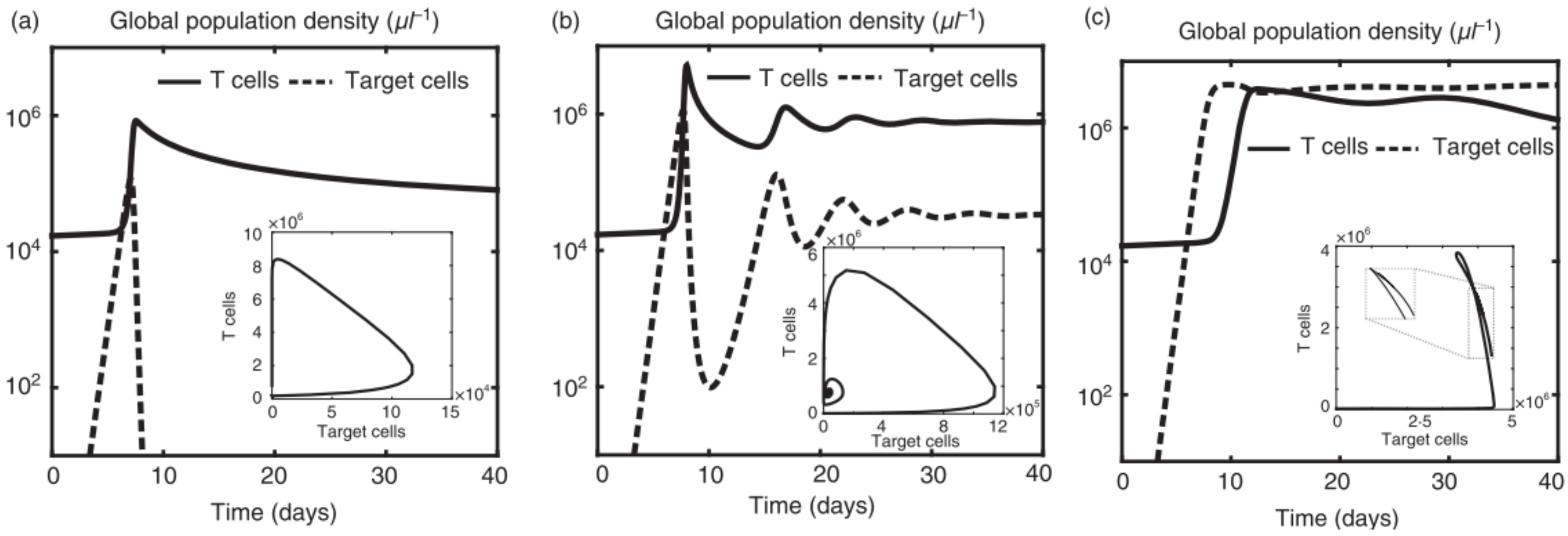
Model reproduces observed biological behaviors

γ, θ: **Large** **Intermediate** **Small**



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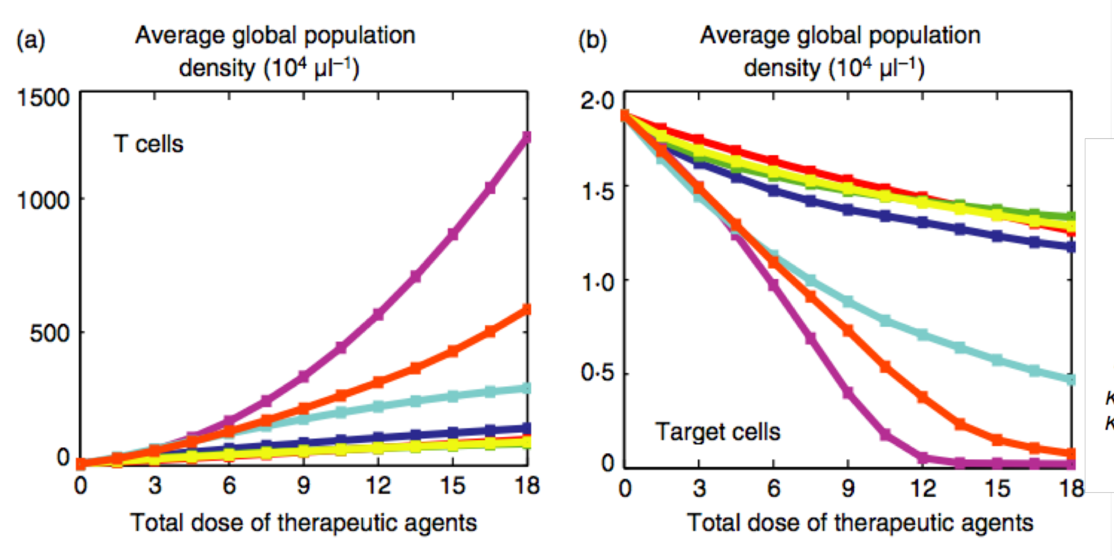
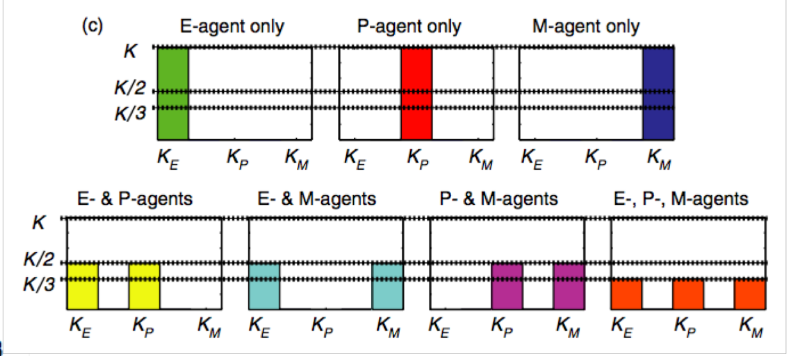
Predicting efficacy of immunotherapeutic agents





Combination of P-agents and M-agents is most effective immunotherapy

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Clinical Significance

- P = *antigen-independent proliferation*
- M = *stabilize the memory pool*
- Possible agents in clinical setting?
  - Homeostatic cytokines: IL-7, IL-15
  - IL-7, IL-15 shown to promote formation of memory CD8 T cells *in vivo*

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