A Compartmental Model of T-cell Activation and Deactivation

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Abstract

Immunotherapy:

- Aim: help CD8+ T-cell fight cancer
- 1st Activation: T-cell Receptor (TCR)
- 2nd Activation: costimulatory receptor (CD28)
- Intercellular protein signaling pathways
- Proteins Akt and PLC-g responsible for expression of main proliferation gene IL-2

Stopping Signals[5]:

- Inhibitory Receptors(CTLA-4, PD-1) block signals
- Immunotherapy introduces drugs that block these inhibitory receptors

Our Goal[4]:

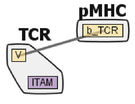
- Model the major signaling proteins in the T-cell
- Simulate using different initial conditions
- Provide a way to investigate how a T-cell responds to immunotherapy drugs

Methods

Create Model using BioNetGen[5]

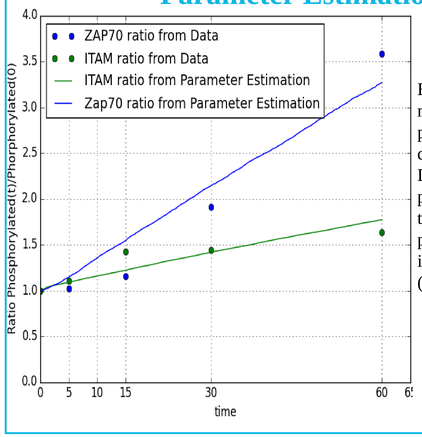
```
begin molecule types
pMHC(b_TCR)
TCR(V,ITAM~U~P)
end molecule types

begin seed species
pMHC(b_TCR)@Tcell_PM
TCR(V,ITAM~U)@Tcell_PM
end seed species

begin reaction rules
Rule1: pMHC(b_TCR) + TCR(V) <->
            pMHC(b_TCR!1).TCR(V!1)   pMHC_on, pMHC_off

Rule2: pMHC(b_TCR!1).TCR(V!1,ITAM~U) ->
            pMHC(b_TCR!1).TCR(V!1,ITAM~P) Lck_phos
end reaction rules
```

Input:
2 molecule types
2 seed species
2 reaction rules
Output:
5 possible species
5 different reactions
Contact Map



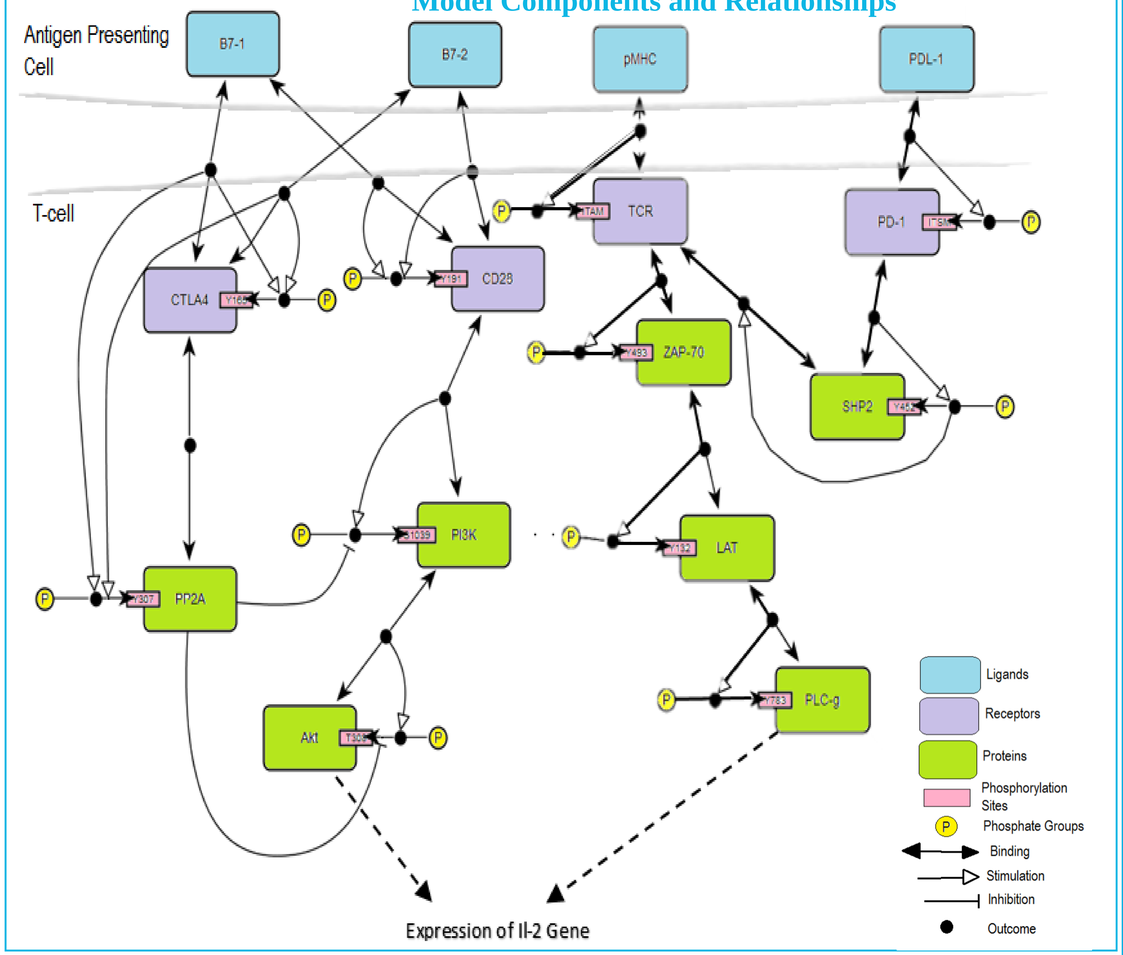
Run Parameter Estimation and Simulation with Copasi[2]

Parameter Estimation



For Parameter Estimation, we fit our model to phosphoproteomics data.[1]
Data given in phosphorylation at time t over phosphorylation at initial time (error bars excluded)

Model Components and Relationships



Expression of IL-2 Gene

Il-2 Expression Conditions:

- PLCg only → IL-2 expression
- PLCg and Akt → IL-2 expression
- Akt only → no IL-2 expression

Tested Formulas:

$$f : \mathbb{R}^2 \to \mathbb{R}$$

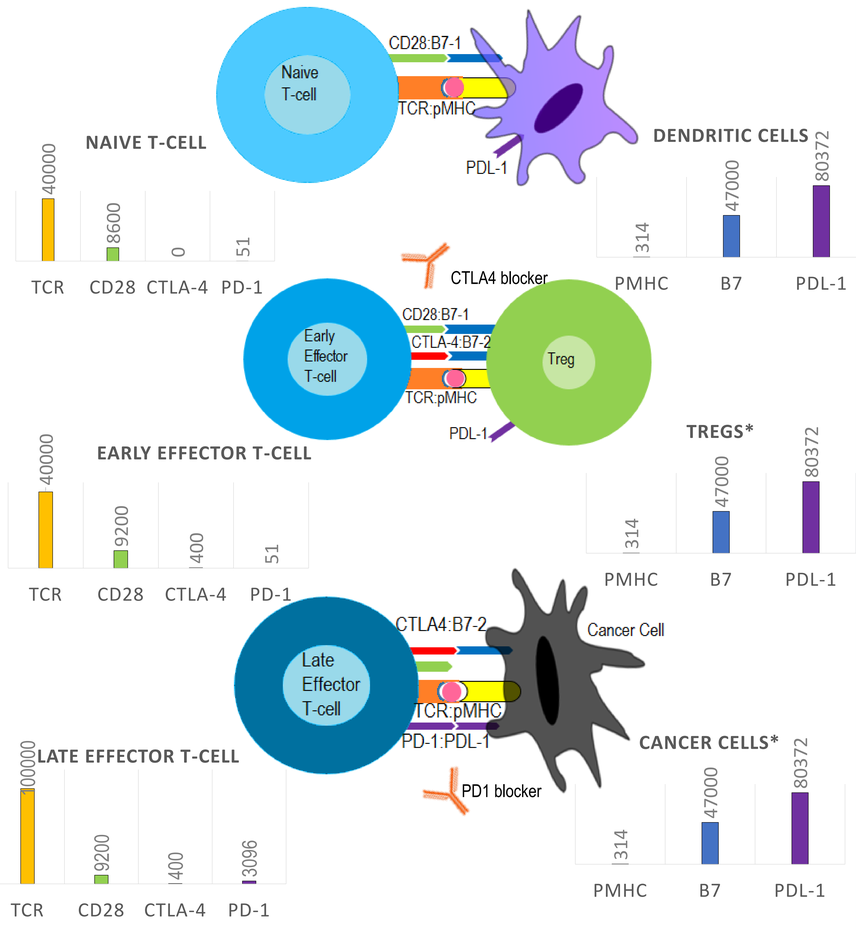
$$f(\mathrm{Akt}, \mathrm{PLC}\gamma) = \alpha \cdot \mathrm{PLC}\gamma + \beta \cdot \mathrm{PLC}\gamma \cdot \mathrm{Akt}$$

$$f(\mathrm{Akt}, \mathrm{PLC}\gamma) = \alpha \frac{\mathrm{Akt}^n}{\mathrm{Akt}^n + k_{D,\mathrm{Akt}}} \frac{\mathrm{PLC}\gamma^n}{\mathrm{PLC}\gamma^n + k_{D,\mathrm{PLC}\gamma}}$$

Data[6]:
Female Mice T-cells were stimulated at different initial conditions and IL-2 levels were evaluated using an ELISA kit.

Initial Conditions	molecules of IL-2/cell after 48 hr
nothing	0
TCR activation	111622
TCR activation and CTLA4	38799
TCR and CD28 activation	1589277
TCR and CD28 activation and CTLA4	559605

Various Simulation Initial Conditions



*Estimate

Selected References

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