Individual Meeting - Ramya (Meeting 1) – 08/29/2025

Goal (Meeting): Discuss topics Ramya missed during the OOC+ABM small group meeting on 08/29/2025 and provide initial guidance to introduce her to the project.

Overview (current LN-ABM):

- **Goal (Model):** Develop an agent-based model (ABM) of two draining lymph nodes (a primary site exposed directly to antigen and a distant site influenced by systemic signals). The model simulates T cell activation, effector expansion, exhaustion, checkpoint blockade, and memory formation under inflammatory and suppressive conditions. By comparing local and distal sites, it is designed to study the abscopal effect (how local immune activation propagates to distant nodes to generate systemic anti-tumor immunity).
- **Agents + Entities in the Model**
  - Dendritic Cells (DCs): arrive at each lymph node with an "antigen amount." After a delay (dwell_steps), they mature and stimulate T cells.
  - T Cells – exist in five compartments:
    - Naïve
    - Activated
    - Effector ($CD8^+$ cytotoxic)
    - Exhausted (dysfunctional)
    - Memory (long-lived)
  - Each pool is updated over time based on biological rules.
- **Key Dynamics (per time step, called a "tick")**
  - DCs arrive at the lymph node and are placed in a queue.
  - Once they've matured (after *dwell_steps*), their antigen amount contributes to T cell activation.
  - Contextual cytokines at each site (IFN-I, IL-12, IL-10, TGF-β) modulate how effective antigen stimulation is.
  - An activation score is calculated, and it drives:
    - Naive → Activated transition
    - Proliferation of activated and effector cells
    - Fate decisions: Effector → Memory or Effector → Exhausted
    - If PD-1 blockade is ON, exhausted cells can refunctionalize
  - A fraction of effector T cells exit the lymph node to go act on tissue (e.g., kill tumor cells).
  - T cells in each compartment also undergo natural death (contraction), with rates specified for each type.

Parameter Table Instructions

All biological and control parameters for the model are defined in the parameter file (*LN Params*). These are initially inform
|ed by values from the literature. Below is a reference table to guide you in identifying what you should be looking for and completing. **Important!** Be sure to include units for every parameter. We need to avoid comparing values that are expressed in different units (e.g., per hour vs. per minute)!

LN Params:

Parameter	Biological Role	Modeling Purpose	Default Value	Reference(s)
dwell_steps	DC maturation delay	Time DCs spend in LN before presenting antigen to T cells	20 - 40 hours	Ref 1, Ref 2,
k_prime	Antigen activation gain	Controls how strongly antigen contributes to activation signal	0.02 - 0.1 reciprocal	Ref 1, Ref 2, Ref 3

			seconds (s^{-1})	
ctx_ifnI_gain	IFN-I co-stimulation	Models pro-inflammatory context enhancing priming		
ctx_il12_gain	IL-12 co-stimulation	Boosts antigen-driven activation via DC/T cell interface		
ctx_il10_penalty	IL-10 suppression	Reduces effective activation in anti-inflammatory environments		
ctx_tgfb_penalty	TGF-β suppression	Mimics Treg/immune suppression at LN level		
N_naive_init	Naive T cells per LN	Starting pool of unprimed T cells		
N_activated_init	Activated T cells	Initial number of T cells undergoing activation		
N_effector_init	Effector T cells	Initial number of cytotoxic T cells ($CD8^+$ Teff)		
N_exhausted_init	Exhausted T cells	Initial number of PD-1^+ dysfunctional T cells		
N_memory_init	Memory T cells	Initial number of long-lived protective T cells		
p_naive_to_activated	Naive → Activated rate	Scales with activation signal; base conversion rate		
p_activated_to_effector	Activated → Effector	Transition rate from recently primed to cytotoxic state		
p_effector_to_memory	Effector → Memory	Low-rate transition, more likely under declining antigen		
p_effector_to_exhausted	Effector → Exhausted	Rate of exhaustion due to chronic stimulation		
p_exhausted_to_effector	Exhausted → Effector	Recovery under PD-1 blockade (refunctionalization)		
prolif_activated	Activated T cell expansion	Antigen-driven clonal expansion (modulated by act level)		
prolif_effector	Effector T cell expansion	Effector expansion under strong activation		
death_naive	Naive cell death	Background turnover of unactivated T cells		
death_activated	Activated cell death	Post-activation contraction or attrition		
death_effector	Effector death rate	Short-lived effectors are lost without stimulus		
death_exhausted	Exhausted cell loss	Dysfunctional cells have finite lifespan		
death_memory	Memory cell attrition	Memory T cells are long-lived but not immortal		
pd1_on	PD-1 blockade toggle	Turns immune checkpoint inhibition ON/OFF		
pd1_blockade_strength	PD-1 block efficacy	Controls how strongly therapy shifts exhaustion dynamics		
egress_rate	Effector exit to tissue	Per-tick fraction of effectors leaving LN to reach tumor		
homing_primary_bias	Trafficking bias	% of egressed effectors that return to *their own* tumor		
tiny	Numerical safety constant	Avoids division-by-zero errors in soft saturations		

To-Do for Next Meeting:

- Begin populating parameter values in **LNParams**
- Review and understand each parameter's biological role and modeling purpose

Future Steps:

- Sensitivity analysis
- Writing opportunities (possibly a review article, we can definitely discuss this more!)