Discussion OOC + ABM (meeting 09/10/2025)

1. ABM model for the one selected chip

Details provided in the ODD document sent on 09/10/2025.

2. Details on the problem, approach, and workflow that can generate enough data for the ABM paper (like with PCA)

Main question: Why does the abscopal effect fail, even when tumor antigen is present?

This suggests that the decisive bottleneck in abscopal failure lies not in the tumor itself, where most current efforts are focused, but in the tumor-draining lymph node (tdLN), where systemic immunity collapses due to missed coordination between dendritic cells (DCs), T cells, and checkpoint dynamics. Thus, we reframe the problem from generating more antigen to optimizing its amplification, harnessing the body's own immune architecture to convert local signals into systemic responses.
By reframing the LN as the decision bifurcation, the model isolates four mechanistic gates where failure can occur:

- Threshold not crossed: too few licensed DCs
- Temporal misalignment: IFN-I peaks vs. DC arrival
- Spatial bias: FRC topology creates dead zones
- Checkpoint dominance: overcrowding drives PD-1/PD-L1–mediated exhaustion

Factor space:

Core factors based on ODD. Each factor maps to at least one of the four core patterns in the model (threshold, timing, topology, checkpoint dominance):

- **Licensing (cDC1 × IFN-I): {on, off} → 2 levels**
  - Encodes the presence/absence of signal (IFN-I) needed for cDC1 licensing; a hard gate for systemic response
- **IFN-I amplitude: {low, mid, high}: {0.3, 0.6, 0.85} → 3**
  - Controls the strength of the licensing field; weak IFN yields partial or failed licensing
- **IFN-I–DC timing offset (peak IFN-I vs DC arrival): {−6 h, 0 h, +6 h} → 3**
  - Encodes temporal alignment; licensing must precede or coincide with DC arrival for success
- **Antigen flux half-life: {short (2–4 h), medium (8–12 h), long (24–48 h)} → 3**
  - Governs how long antigen remains available during DC migration and T cell scanning
- **PD-L1 density (stroma/DC): {10th, 50th, 90th pct of prior} → 3**
  - Represents checkpoint saturation pressure within LN; maps to "checkpoint dominance" failure pattern
- **Egress gate permeability (S1P1 dynamics): {low, baseline, high}: {8 h, 14 h, 22 h} → 3**
  - Controls delay and filtering of effector export; impacts whether amplified clones disseminate
- **FRC topology: {empirical graph A, empirical graph B / synthetic small-world} → 2**
  - Captures spatial wiring of the LN; changes contact probability distributions and microdomain formation

Full factorial: 2×3×3×3×3×3×2 = 972 conditions.

Initial screening LHS + 3 replicates:

We divide the full experiment into blocks based on Licensing.
Block A: Licensing ON

- Represents scenarios where IFN-I licensing occurred → we focus on amplification.
- Design:
  - FRC Topology: Across both (2 topologies)
  - LHS Sampling: 100 combinations of remaining 5 factors
  - Total runs: 2 topologies × 100 LHS samples → 200 runs

Block B: Licensing OFF

- Represents failure to license, where systemic response likely fails.
- Purpose: Characterize bottleneck logic and threshold failure
- Design:
  - FRC Topology: Across both (2 topologies)
  - LHS Sampling: Fewer runs (e.g., 50), since most outcomes will show failure?
  - Total runs: 2 topologies × 50 samples → 100 runs

Therefore with 3 replicates per point:

Block	Licensing	FRC Topologies	LHS Samples	Replicates	Total Runs
A	ON	2	100	3	2 × 100 × 3 = **600**
B	OFF	2	50	3	2 × 50 × 3 = **300**

Total phase 1 runs: **900**

For each point → we calculate mean + SD to flag points with high variance → preliminary PCA/PCR + identify sensitive regions

For high variance points → we'll re-run with 16 replicates to focus specifically on points near transitions zones + bifurcation points (e.g., from tolerance to amplification).

Therefore:

Block	Licensing	FRC Topologies	High-Variance Points	Replicates	Total Runs
A	ON	2	20 (10% of 200 pts)	16	20 × 16 = 320
B	OFF	2	10 (10% of 100 pts)	16	10 × 16 = 160

Total phase 2 runs: **480**

Phase	Purpose	Total Runs
Phase 1	Broad sampling + variance check	900
Phase 2	High-res runs of key regions	480
Total		**1,380**

Raw outputs:

- T cell Activation Score: Reflects quality of signal integration
- Peak T Cell Count: Total activated T cells across simulation
- Cytokine Field Dynamics**:** Spatial and temporal maps of IFN-I, IL-12
- Egress Percentage: Fraction of T cells successfully exiting the LN
- Exhaustion Ratio: Fraction of activated T cells entering exhaustion

- Contact Metrics: Frequency, duration, and density of DC–T cell contacts
- Time-to-Activation: Delay between antigen arrival and T cell priming

Derived features	Computation	Definition
Amplification index	z(AUC_activated) − z(Exhausted/Activated) + z(Egress%)	Composite score for T cell amplification success
Licensing efficiency	Fraction(cDC1 licensed by 6 h)	Early innate trigger effectiveness
Temporal alignment	Cross-correlation(IFN-I, DC-arrival) lag	Synchronization between IFN-I release and DC influx
Topological advantage	Encounter-rate percentile vs. null-walk	How well spatial topology enhances encounters vs random walk
Checkpoint pressure	∫ (PD-1 occupancy × contact density) dt	Aggregate burden of inhibitory checkpoint signals
Primary endpoints	**Type**	**Definition**
Abscopal success	Binary (Yes/No)	Amplification Index > θ_1 AND Egress% > θ_2 within 48–72 h
Systemic potency	Continuous Score	Weighted sum: Normalized AUC + Egress% + (1 − Exhaustion)
θ_1, θ_2	Scalar thresholds	Defined from Youden-optimized cut points on ROC from Phase 1, locked before Phase 2