**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.

1. **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 > θ₁ **AND** Egress% > θ₂ within 48–72 h |
| **Systemic potency** | Continuous Score | Weighted sum: Normalized AUC + Egress% + (1 − Exhaustion) |
| **θ₁, θ₂** | Scalar thresholds | Defined from **Youden-optimized cut points** on ROC from Phase 1, locked before Phase 2 |

configs/

LN\_ABM\_BlockA\_empirical\_A\_sample000\_rep1.json

LN\_ABM\_BlockA\_empirical\_A\_sample000\_rep2.json

LN\_ABM\_BlockA\_empirical\_A\_sample000\_rep3.json

LN\_ABM\_BlockA\_empirical\_A\_sample001\_rep1.json

….

LN\_ABM\_BlockA\_empirical\_A\_sample049\_rep1.json

blockA.yaml

YAML 🡪JSON python script

+

LHS

blockB.yaml

blockA\_highvar.yaml

blockA\_highvar.yaml

Broad exploration to flag high variance + transition zones (e.g., mean + SD, PCA, QC, parameters vs. outcomes)

* Dimensionality reduction (PCA/UMAP on derived features 🡪 see if “success vs. failure” separates in reduced space)
* Clustering/phenotyping (k-means, DBSCAN or hierarchical clustering on features 🡪 discover immune “phenotypes”)
* Sensitivity analysis (Sobol/eFast) 🡪 rank most influential parameters)
* Boundary mapping (identify bifurcation zones 🡪 where a small parameter change flips success to failure, and vice versa)
* Predictive modeling (random forest, neural networks 🡪 predict endpoints from parameters)

Python script (feature-extraction pipeline)

ABM

Raw outputs/run (HDF5)

* Time series (T-cell counts, contact events)
* Log files / observable at each tick

+ linked back to their JSON config.

Complex derived features (CSV):

Amplification index, temporal alignment score, checkpoint pressure…)

Summary endpoints (abscopal success, systemic potency)