Causal inference analysis of live cell imaged confrontation assays with agent-based modelling

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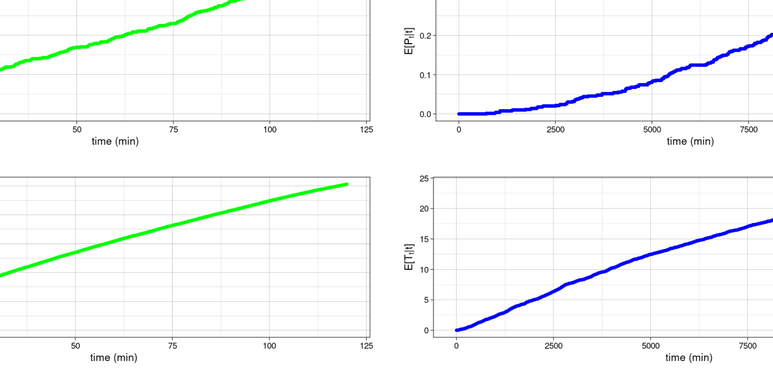
Introduction

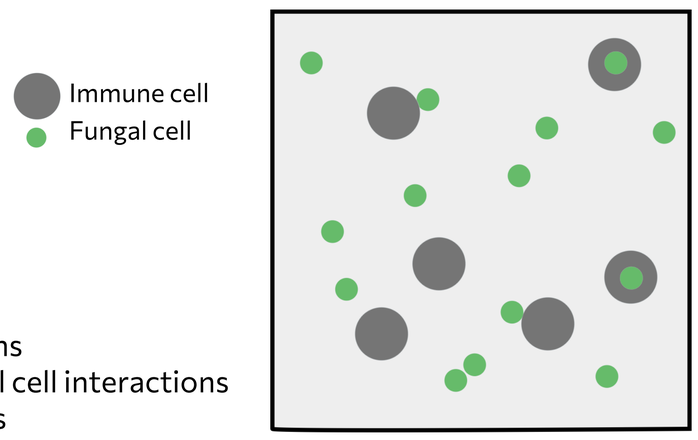
Here we combine agent-based models (ABMs) with Dynamical Bayesian Networks (DBNs) [1] to analyse the cell track data in confrontation assays. DBNs can in principle describe the heterogeneity that is often observed in cell tracks [2] is caused by previous interactions or natural variability and even find causal interactions between different observables. Limitations are the amount of tracks normally available for each time point in live cell imaging, that the cells disappear from the field of view and that interactions occur because of the spatial distribution of the system rather than internal cell states. Therefore, we here use simulated data of a confrontation assay containing neutrophils and fungal cells based on an agent-based model [3]. In this model we can introduce causal relationships and remove them to investigate how these are represented in the DBN. We give an example how DBNs can identify a causal relationship between immune cell-fungal touching and the probability of individual immune cells to phagocytose fungal cells. We especially look at the possible dependencies that are introduced by spatial dynamics compared to the intrinsic causal effects that we introduce in the ABM.

t: discrete time index with range $t \in [0, t_{\max}]$
T_t: number of fungal cell touchings per immune cell until time t
$\hat{T}$: additional touching event occuring between t and $t+1$
P_t: number of phagocytosis events per immune cell until time t
$\hat{P}$: additional phagocytosis event occurring between t and $t+1$



Agent-based model and simulations

- 2D environment
- Immune cells
- Fungal cells
- 500 cells of each type
- Simulated for 2 h
- Time step: 0.01 s
- C++ implementation



- Provides track files with
  - ✓ Immune cell positions
  - ✓ Immune cell – fungal cell interactions
  - ✓ Phagocytosis events

- Control simulation
  - ✓ All immune cells are activated at the start of the simulation
  - ✓ Phagocytosis occurs throughout the simulation
- Causal simulation
  - ✓ Immune cell activation necessary for phagocytosis
  - ✓ No immune cells are activated at the start of the simulation
  - ✓ At least one touching event necessary for immune cell activation
  - ✓ Multiple touchings increase activation probability

Network inference

Model selection

- The dependence of $\hat{T}$ and $\hat{P}$ on T_t, P_t and t is determined by logistic regression $p(\hat{T}=1) = S_{\hat{T}}(\pi_T + \alpha_T P_t + \beta_T T_t + \gamma_T t)$, $p(\hat{P}=1) = S_{\hat{P}}(\pi_P + \alpha_P P_t + \beta_P T_t + \gamma_P t)$
- The terms T_t and P_t are intrinsic causal factors, specific for each immune cell
- The term t is an extrinsic factor that captures changes on the population level
- All possible linear combinations of the factors are tried
- Model selection is made based on the Bayesian information criterion (BIC)
- Testing the method by generating non-spatial data according to:

$$T_{t+1} = T_t + \hat{T}, \qquad p(\hat{T}=1) = \pi_T,$$
$$P_{t+1} = P_t + \hat{P}, \qquad p(\hat{P}=1) = \pi_P - \pi_P(1-\mathrm{e}^{-\alpha P_t}) + (1-\pi_P)(1-\mathrm{e}^{-\beta T_t})$$

- $\pi_P = \pi_T = 0.05, \alpha = 0.00$ and $\beta = 0.00$ is the non-spatial control case
- $\pi_P = \pi_T = 0.05, \alpha = 0.05$ and $\beta = 0.01$ is the non-spatial, causal case

Best fitting network, non-spatial control

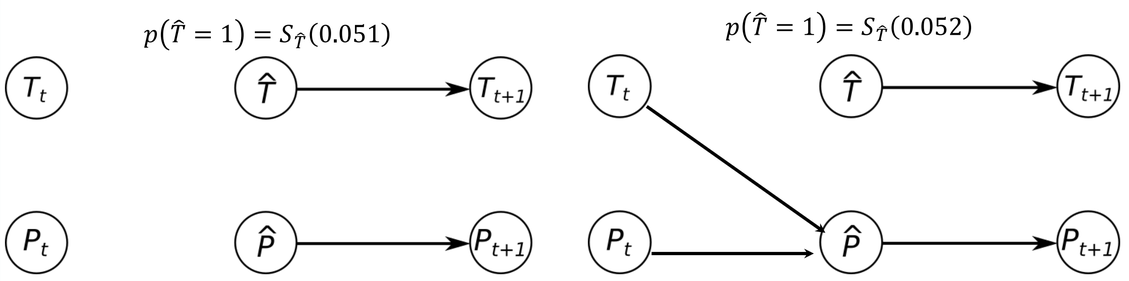
$p(\hat{T}=1) = S_{\hat{T}}(0.051)$

$p(\hat{P}=1) = S_{\hat{P}}(0.05)$

Best fitting network, non-spatial causal

$p(\hat{T}=1) = S_{\hat{T}}(0.052)$

$p(\hat{P}=1) = S_{\hat{P}}(0.052 - 0.048P_t + 0.0096T_t)$



Inferred networks from ABM simulations

Best fitting network, ABM control

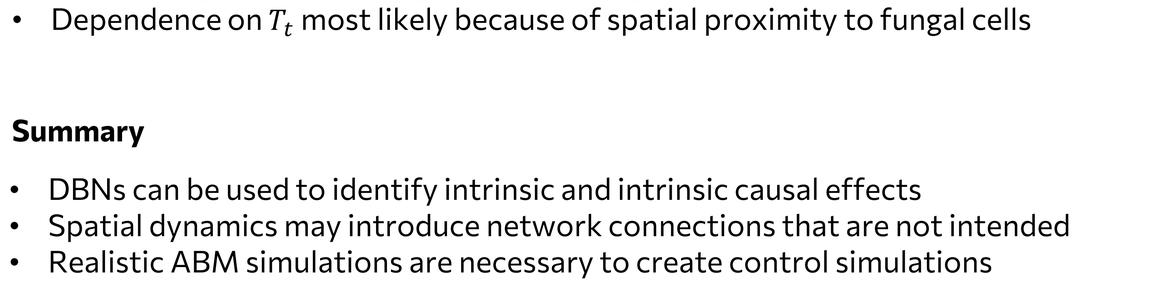
$p(\hat{T}=1) = S_{\hat{T}}(0.0071 + 0.011T_t - 0.0084t)$

$p(\hat{P}=1) = S_{\hat{P}}(8.67 \cdot 10^{-6})$

Best fitting network, ABM causal

$p(\hat{T}=1) = S_{\hat{T}}(0.0027 + 0.026T_t - 0.00013t)$

$p(\hat{P}=1) = S_{\hat{P}}(1.5 \cdot 10^{-5} + 0.036T_t)$



- $\hat{P}$ follows the expected dependencies
- $\hat{T}$ unexpectedly depends on t and T_t
- Diminishing amount of fungal cells as they get phagocytosed explains t dependence
- Dependence on T_t most likely because of spatial proximity to fungal cells

Summary

- DBNs can be used to identify intrinsic and intrinsic causal effects
- Spatial dynamics may introduce network connections that are not intended
- Realistic ABM simulations are necessary to create control simulations

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References
[1] Eldawlatly *et al.* 2010. *Neural Comput.* 22(1):158-189.
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