Evidence for a Rac-inhibitor: Data, Model, and Cell Migration Simulations

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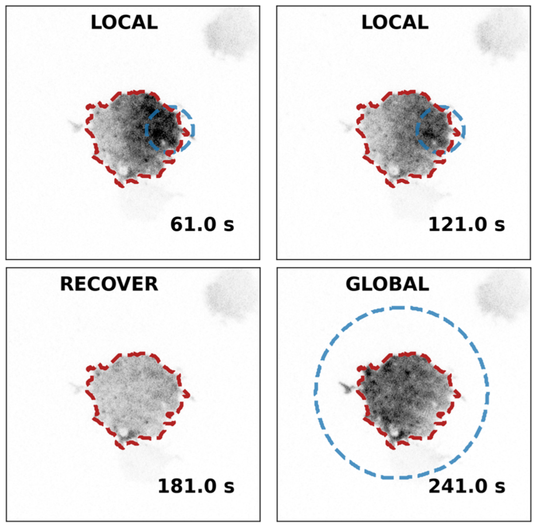
Background

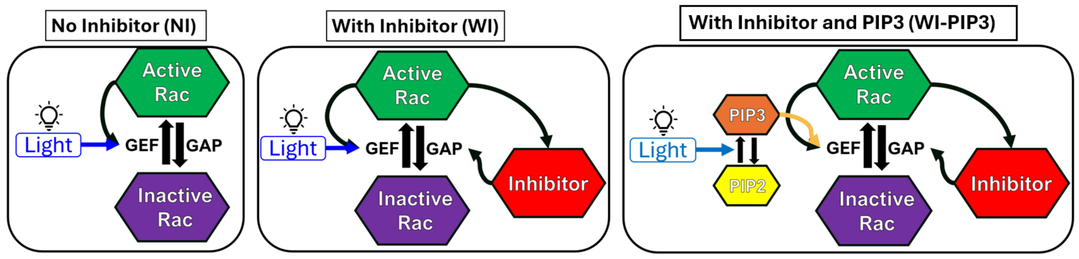
- Rac drives cell protrusion and motility at the leading edge of neutrophils.
- Neutrophils adapt to stimuli, including chemical gradients and obstacles.
- Recent optogenetic data suggest that a Rac-inhibitor is critical for guiding cell behaviour [3].
- This study revises a basic model (Wave-Pinning) [1] using time-dependent data from latrunculin-treated cells to test the inhibitor hypothesis.

Optogenetic Stimulation

- Local PI3K recruitment increases Rac briefly, then decreases, suggesting a local inhibitor.
- Stimulus-naive areas show stronger responses to subsequent global stimulation, supporting the presence of the inhibitor.

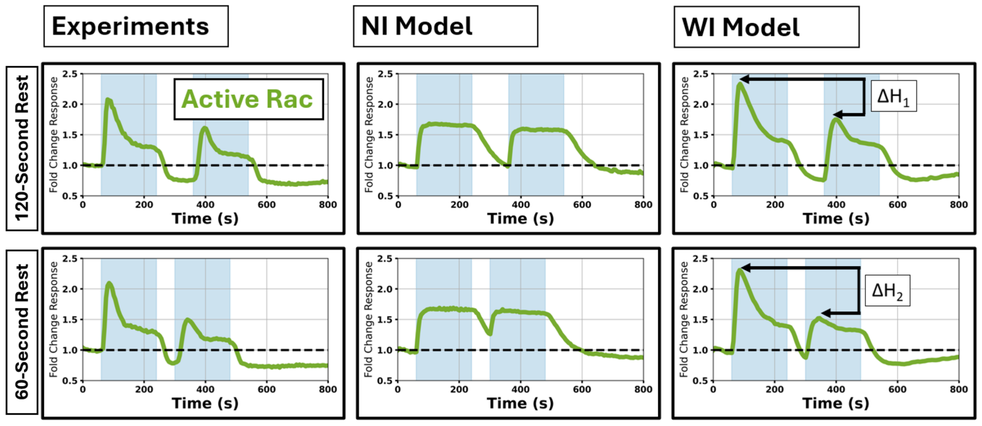


Models



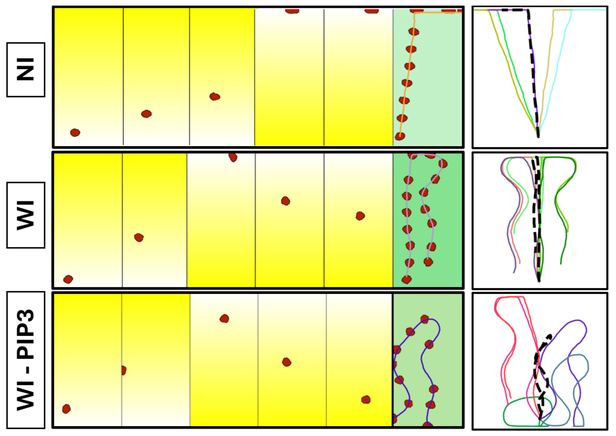
- PDE-based models simulate Rac dynamics along the cell edge (1D, periodic).
  - **NI:** No inhibitor (3 variables).
  - **WI:** With inhibitor (4 variables).
  - **WI-PIP3:** With inhibitor and PIP3 (5 variables).

Time Dependent Rac Dynamics



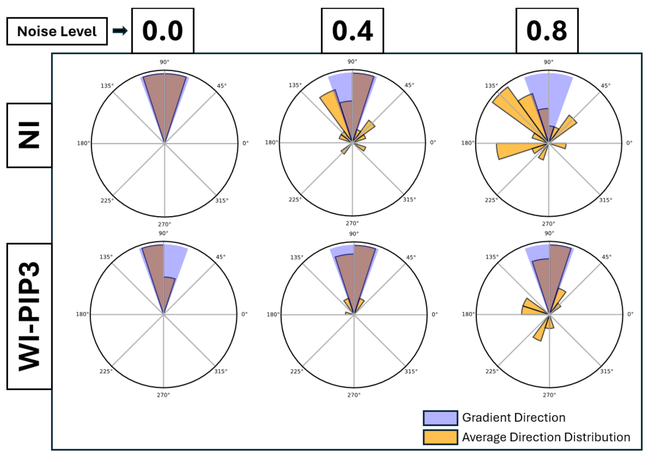
- WI model reproduces Rac's adaptive response in 2-pulse experiments; NI does not.
- Longer rest periods increase the Rac response to the second pulse.

Gradient Reversal Simulation



- In noise-free gradients, all models accurately align to the gradient direction.
- Only WI and WI-PIP3 detect gradient reversal.

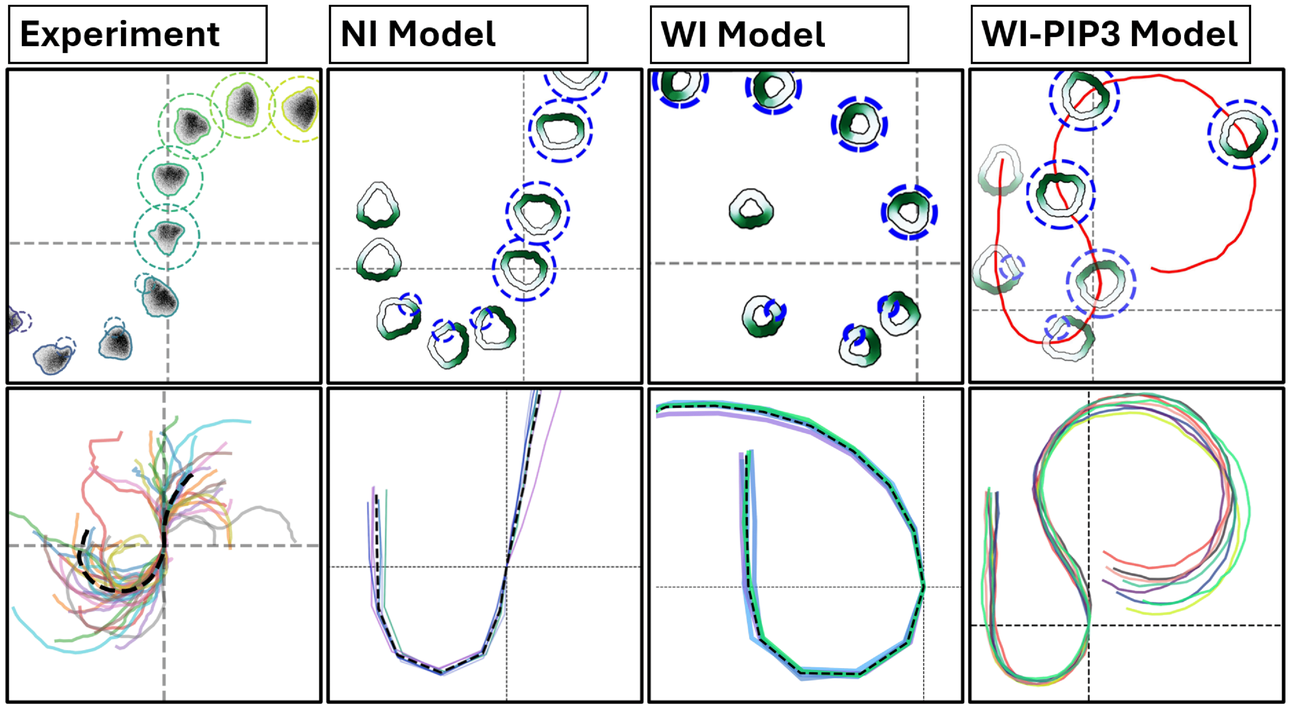
Model Comparison to Follow Chemical Gradient



- WI-PIP3 model maintains better alignment than the NI, particularly as the noise increases. The results are based on 20 simulation runs per configuration.

Simulating Neutrophil Motility

- Another result in [3] revealed unexpected behaviours: localized Rac activation followed by global stimulation caused cell reversals (Figure 4). Initially, the cell rotates counterclockwise to follow the local stimulation. However, when globally stimulated, the cell reverses its rotation direction.
- We simulated cell motility using PDE-based Rac dynamics along the cell edge in Morpheus [2]. Rac activity increases the probability of edge protrusion, indirectly representing F-actin persistence. Simulated trajectories were compared to experimental neutrophil migration data from Town & Weiner [3]



Significance

- Models reveal how local negative feedback enables adaptive motility and polarization.
- This framework integrates experimental insights with predictive simulations.
- Findings improve our understanding of cellular decision-making, relevant for development, immunity, and metastasis.

References

[1] Mori et al (2008) Biophysical Journal.
[2] Starruß et al (2014) Bioinformatics.
[3] Town & Weiner (2023) PLoS Biology.

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