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Simulation-Based Analysis of *in Situ* Cellular Motility

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A fundamental challenge in simulation-based investigation of biological systems is deciding how detailed to make the simulation. Here we present a methodology that uses an automated simulation parameterisation technique to guide simulation development to an appropriate level of abstraction. We demonstrate the methodology in the context of simulating cellular motility. Recent advances in modern day imaging technology allow for the *in situ* examination of individual cells' migration through tissues. Complex and sometimes highly coordinated patterns have been observed, such as the swarming response of neutrophils to sterile tissue injury [1]. It is not clear what factors drive these responses, but the detailed single-cell spatial-temporal location data that these microscopy technologies provide permits a simulation-based analysis approach.

Our simulation-based methodology attempts to recreate the dynamics observed *in situ* by providing a platform wherein models of cellular behaviour can be created and calibrated, and evaluated against real-world data sets. Our methodology is depicted in figure 1. Through an agent-based simulation approach cells are explicitly represented as individuals with unique internal states and locations in a spatial environment. A model of the behavioural responses of simulated cells to the stimuli they observe in their local environments can be specified. The location of each cell in the environment over time can be tracked, permitting the construction of a statistical profile of their motility dynamics. Similar profiles are constructed for the *in situ* data, and their direct comparison allows for the evaluation of how well the behavioural responses programmed into simulated cells reflect the real-world dynamics.

Accurately capturing real-world dynamics requires both an appropriate model, and appropriate parameters for that model. We employ multi-objective optimisation to identify the parameter sets that, given a particular model of cellular behaviour, best align simulation dynamics with those observed *in situ*. The metrics comprising the statistical profile, which might include the speeds cells move at and the rotational velocities at which they change direction, form objectives for calibration. NSGA-II [2] is used as our multi-objective optimisation algorithm. Where NSGA-II is unable to find parameter values that align simulation dynamics with those observed *in situ*, one may conclude that the underlying model of cellular behaviour is incorrect.

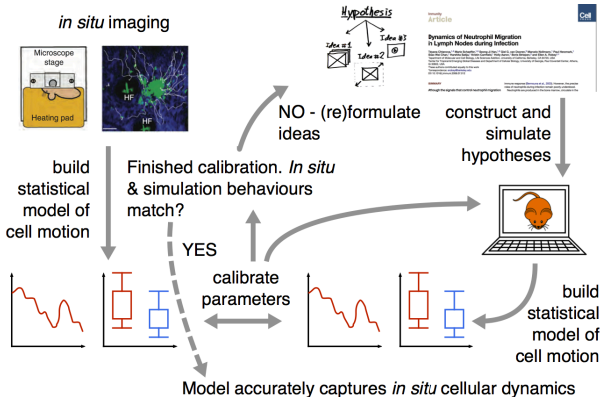

Figure 1: Our simulation-based methodology for conceiving and evaluating hypotheses concerning the factors driving cell motility as observed through *in situ* imaging.

Thus far we have used this methodology to analyse non-directional neutrophil motility in the extra-vascular dermis of the mouse ear, in absence of tissue injury. We have concluded that neutrophils do not follow a Levy-flight motility pattern, wherein cells move in a uniformly random direction for a distance drawn from a long-tailed distribution. Rather, a model wherein changes in neutrophil movement direction are drawn from normal distributions with zero mean, and speeds are drawn from normal distributions unique to each cell accurately reflects the observed *in situ* dynamics.

Having established a proof of principle for our methodology, further work will examine the factors driving neutrophil swarming in response to sterile tissue injury. Moreover, the methodology has potential application in other domains, aiding in model selection and informing the level of detail required to accurately capture the biology.

References

[1] Chtanova, T., *et al.* (2008). Immunity 29:487-496.
[2] Deb, K., *et al.* (2002). IEEE Trans on Evo Comp, 6(2):182-197.

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