# Decoding and propagating inflammatory cues via NF-κB signaling

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**Our immune responses are driven by the dynamic interaction and coordination of immune cells within the tissue. Pro- and anti-inflammatory cytokines regulated at different levels of cellular organization mediate these spatial-temporal interactions, of which the Nuclear Factor kappa B (NF-κB) transcription factor plays a critical role. Upon cytokine stimulation, NF-κB oscillates between the cytoplasm and the nucleus leading to the dynamic transcription of many genes including inflammatory cytokines. A mathematical model demonstrates how this complex positive and negative feedback system in single cells can lead to emergent behaviour at the tissue level.**

***Keywords*** **— NF-κB, receptor, TNFR1, oscillations, TNFα, stochasticity**

## I. Background

The NF-κB family of transcription factors critically regulates innate immune responses and inflammation and has a key role in cell division and apoptosis [1]. NF-κB must decode noisy extracellular cytokine signals and encode intercellular information leading to specific cell fate decisions. NF-κB also regulates the production of cytokines that may lead to the amplification of inflammatory signals. Failure to control these temporal-spatial cues is associated with hyper inflammatory tissue-level responses characteristic to many autoimmune diseases.

Using time-lapse confocal microscopy we study the single cell dynamics of the NF-κB system. We showed that in response to cytokine stimulation, NF-κB oscillates between the cytoplasm and the nucleus and the frequency of oscillations controls target gene expression [2,3]. Oscillations between individual cells appear asynchronous and we hypothesised that this is due to a dual IκB negative feedback that drives cellular heterogeneity and allows robust population responses [4].

By developing a more quantitative picture of single cell NF-κB regulation, we can begin to understand how tissue level inflammatory signalling emerges from the dynamic interactions between individual cells.

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## II. Results

Based on single-cell time-lapse imaging data we developed a new cell model of the NF-κB system. We specifically considered regulation of the system via noisy receptor activation and used the model to probe the ability of the system to respond to pulsatile stimulation [3]. Additionally, a putative autocrine/paracrine NF-κB dependent cytokine feedback was considered to investigate the amplification of inflammatory signals.

Secondly, a reaction-diffusion model was developed by coupling many single-cells via paracrine signalling. The model shows potential for the generation of cytokine waves that propagate inflammatory signals through the tissue [5]. With only a small number of cytokine molecules produced in small intracellular volumes, intricate stochastic dynamics of receptor activation and cytokine diffusion can either amplify or terminate the transmitted signal.

## III. Conclusion

Multi-scale mathematical modelling of noisy inflammatory signals in tissues will allow a better understanding of inflammatory processes.

## References

[1] Hayden S, Ghosh G, (2008). Shared Principles in NF-kB Signalling. *Cell*, *132*(3), 344-362. http://www.sciencedirect.com/science/article/pii/S009286740800120

[2] Nelson DE, Ihekwaba AEC, Elliott M, Johnson JR, Gibney CA, Foreman BE, Nelson G, See V, Horton CA, Spiller DG, Edwards SW,. McDowell HP, Unitt JF, Sullivan E, Grimley R, Benson N, Broomhead D, Kell DB, and White MRH (2004). Oscillations in NF-κB Signaling Control the Dynamics of Gene Expression. *Science*, 306(5696) 704-708. http://www.ncbi.nlm.nih.gov/pubmed/15499023

[3] Ashall L, Horton CA, Nelson D, Paszek P, Harper CV, Sillitoe K, Sheila R, Spiller DG, Unitt JF, See V, Rand D, Broomhead D, Kell DB, and White MRH (2009). Pulsatile Stimulation Determines Timing and Specificity of NF-κB-Dependent Transcription. *Science, 324(5924), 242-246. http://www.ncbi.nlm.nih.gov/pubmed/19359585*

[4] Paszek P, Ryan S, Ashall L, Sillitoe K, Haper CV, Spiller DG, Rand DA, White MRH (2010). Population robustness arising from cellular heterogeneity.*PNAS 107(25) 11644-11649 http://ateson.com/ws/r/www.pnas.org/content/107/25/11644.full*

[5] Yde P, Mengel B, Jenson MH, Krishna S, Trusina A, (2011). Modelling the NF-kB mediated inflammatory response predicts cytokine waves in tissue.BMC Systems Biology 5(1) 115. http://www.biomedcentral.com/1752-0509/5/115