The 9th International Conference on Systems Biology ICSB2008
August 22-28, 2008 Göteborg (Gothenburg) Sweden
1401503

Noise from spatial heterogeneity changes signal amplification magnitude and increases the variability in dose responses.

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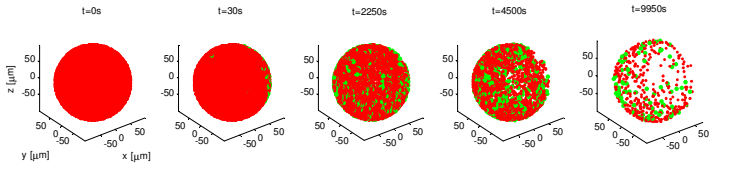
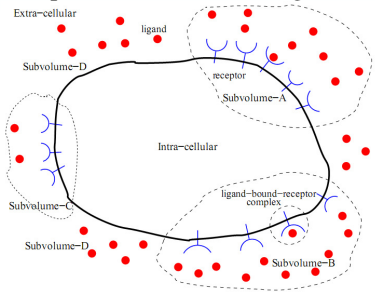
Objectives

In most molecular level simulations, spatial heterogeneity is neglected by the well-mixed condition assumption. However, the signals of biomolecular networks are affected from both time and space, which are responsible for diverse physiological responses. To account the spatial heterogeneity in the kinetic model, we consider multiple subvolumes of a reaction, introduce parameters representing transfer of ligands between the volumes, and reduce this to an error-term representing the difference between the well-mixed condition and the actual spatial factors. The error-term approach allows modelling of varying spatial heterogeneity without increasing computational burden exponentially.

The effect of varying this term, δ, between 0 (well-mixed) and 1 (no mixing) and of adding noise to the kinetic constants was then investigated and correlated with knowledge of the behaviour of real systems and situations where network models are inadequate. The spatial distribution effects on the epidermal growth factor receptor (EGFR) in human mammary epithelial tissue, which is involved in proliferation and tumorigenesis, are studied by introducing noisy kinetic constants.

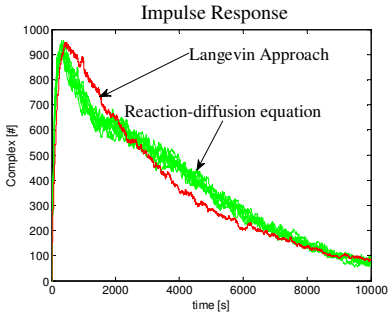


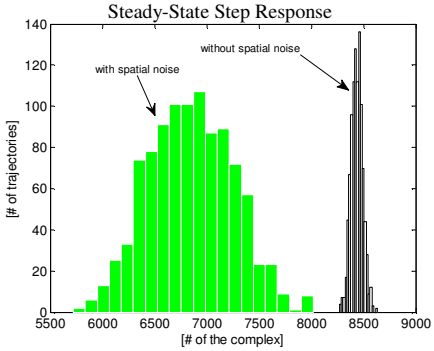
Ligand (red), Ligand-Receptor Complex (green), Receptor (non-uniformly distributed, not-shown)



$$
\begin{aligned}
P\left(dR=-1\right) &= k_{\text{on}}\left[RL - R_A\left(L_B+L_C+L_D\right) - R_B\left(L_A+L_C+L_D\right)\right. \\
&\quad \left. -R_C\left(L_A+L_B+L_D\right) - R_D\left(L_A+L_B+L_C\right)\right] + k_t R dt \\
&= k_{\text{on}}\left(1-\delta\right)RL + k_t R dt
\end{aligned}
$$

Results





$$
\begin{aligned}
dR &= \left[-k_{\text{on}}(1-\delta)RL - k_t R + k_{\text{off}}C + Q_R\right]dt \\
&\quad + \sqrt{k_{\text{on}}(1-\delta)RL + k_t R + k_{\text{off}}C + Q_R}\; dw_R \\
d\delta &= a_\delta(T,R,L)dw_\delta
\end{aligned}
$$

The steady-state of the dose response in the EGFR is strongly affected by spatial fluctuations. The ligand-bound receptor is reduced up to 50% from the response without spatial fluctuations and the variance of the steady-state is increased at least 2-fold from the one for no spatial fluctuations. On the other hand, dynamic properties such as the rising time and overshoot are less sensitive to spatial noise.

Conclusions

The EGFR signal transduction pathway may evolve to reduce the effect from the spatial heterogeneity – through active transport mechanisms, or selection to exploit rapidly transported ligands - or have some control architecture - localization of reactions in appropriate sub-domains within the cell - to carefully manage not only timing but also spatial distributions. From the pharmaceutical point of view, since the dose response is significantly diminished by the spatial non-uniformity, to maximise the response not only the amount but also the spatial distribution of the dose must be carefully controlled – targeted to particular cellular domains, having active transport and passive diffusion parameters appropriate for the reactions being manipulated.

Acknowledgements

This work was supported by the Department of Aerospace Engineering, University of Glasgow, Glasgow, UK.

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