An adaptable in silico model of the arachidonic acid cascade

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Eicosanoids are a family of bioactive lipids, derivatives of the polyunsaturated fatty acid arachidonic acid. The intimate involvement of eicosanoids in inflammation motivates the development of predictive *in silico* models for a systems-level exploration of disease mechanisms, drug development and replacement of animal models. Using an ensemble modelling strategy, we developed a computational model of the arachidonic acid cascade. This approach allows the visualisation of plausible and thermodynamically feasible predictions, overcoming the limitations of fixed parameter modelling. A quality scoring method was developed to quantify the accuracy of ensemble predictions relative to experimental data, measuring the overall uncertainty of the process. Monte Carlo ensemble modelling was used to quantify the prediction confidence levels. Model applicability was demonstrated using mass spectrometry mediator lipidomics to measure eicosanoids produced by HaCaT epidermal keratinocytes and 46BR.1N dermal fibroblasts, treated with stimuli (calcium ionophore A23187, ultraviolet radiation, adenosine triphosphate) and a cyclooxygenase inhibitor (indomethacin). Experimentation and predictions were in good qualitative agreement, demonstrating the ability of the model to be adapted to cell types exhibiting differences in arachidonic acid release and enzyme concentration profiles. The quantitative agreement between experimental and predicted outputs could be improved by expanding network topology to include additional reactions. Overall, our approach generated an adaptable, tuneable ensemble model of the arachidonic acid cascade that can be tailored to represent different cell types and demonstrated that the integration of *in silico* and *in vitro* methods can facilitate a greater understanding of complex biological networks.

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