A mathematical model for the role of calcium and cAMP in axon guidance

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The ability for growing axons to locate appropriate spatial targets is an essential part in the formation of correct circuits during neural development. Molecules called guidance cues guide the growth cone of a growing axon. The response of a growth cone to a guidance cue is determined by a complex network of intracellular events. For most guidance cues, two important second messengers within the growth cone are cAMP and calcium. Raising calcium on one side of the growth cone can lead to either attraction or repulsion, though small increases in calcium have different effects to that of large increases. Additionally the baseline calcium level in the growth cone can affect the turning response to a guidance cue. Combined, these elements make it difficult to make predictions about the turning behaviour of a growth cone in response to varied conditions. Additionally, cAMP also has a role in determining the direction of growth cone turning, further adding to the complexity of the system.

Currently there are very few theoretical models of signal transduction in axon guidance. In particular, until now there has been no complete and rigorous model of the underlying mechanisms that cause the response of the growth cone to calcium and cAMP. Thus it has been impossible to make predictions of the turning behaviour of a growth cone under previously untested conditions. Making predictions about growth cone behaviour is critical for understanding the changes that occur during development, and the role that cAMP levels play in recovery from injury.

We have devised and implemented the first mathematical model of the mechanisms underlying calcium and cAMP dependent growth cone turning. The model exposes a simple but elegant signal transduction network that underlies many seemingly contradictory experimental results. The model is able to account
for current experimentally observed behaviours. The signal transduction network is similar to one that has been previously used to model the switch between LTP and LTD, providing an intriguing connection between growth cone guidance and synaptic plasticity.

The model also generates new experimental predictions, which we have tested and confirmed. This strengthens the validity of the model and provides the surprising prediction that decreasing cAMP can cause attraction under certain conditions, which had never previously been reported. This is of great importance in understanding the role of cAMP in development and neural regeneration.