

COMPUTER MODELS OF BACTERIAL CHEMOTAXIS

Over the last 12 years, a range of computer models of the chemotaxis signal-transduction pathway in *E. coli* have appeared. They differ in their comprehensiveness and in the particular parts of the pathway they highlight or the general principles they illustrate. The most significant models in terms of achievement or insight are summarised in the following table:

Model	Description
Bray et al. (1993)	The first attempt at a comprehensive model (BCT program). Excitation response simulated, but not the adaptation response (CheR and CheB are present but have no activity, although CheB acts as a phosphate sink). Ternary receptor complex built from individual components. Phenotypes of 33 out of 41 mutants accurately reproduced.
Bray and Bourret (1995)	An updated version of BCT, incorporating a more biologically realistic model for formation of the ternary receptor complex, with binding affinities optimised by an evolutionary algorithm.
Hauri and Ross (1995)	Kinetic parameters based on experimental measurements, but adjusted (fine-tuned) by a multiple-well optimisation technique. The first model to simulate exact adaptation to both attractant (aspartate) and repellent (Ni^{2+}) stimuli, although only weak scaling of adaptation time with stimulant concentration emerges.
Barkai and Leibler (1997)	The concept of robustness (system-invariant properties) in biochemical networks introduced, showing how it may arise in bacterial chemotaxis through activity-dependent kinetics. A three-component model consisting of receptor complexes, CheR and CheB. Simulations show that precision of adaptation is a robust property, while adaptation time is not, and that adaptation time is inversely proportional to receptor-complex activity.
Spiro et al. (1997)	Simplified three-methylation-state model, fine-tuned by trial and error, simulates ramp, step and saturation responses to aspartate, although the major focus is on an analysis of the gain (sensitivity) of the system.
Levin et al. (1998)	Receptor-modification reactions catalysed by CheR and CheB incorporated in BCT to explore the consequence of variation in protein expression and the phenomenon of non-genetic individuality.

Morton-Firth et al. (1999)	<p>The first stochastic simulation of bacterial chemotaxis, using the StochSim program.</p> <p>Activity of receptor complexes determined by free-energy changes due to both ligand binding and changes in methylation state.</p> <p>Robust adaptation achieved through CheR binding exclusively to inactive receptor complexes and (phosphorylated) CheB to active ones.</p> <p>Simulations of step responses to aspartate analysed for temporal changes in methylation states, and the question of local versus global adaptation explored.</p>
Shimizu et al. (2003)	<p>StochSim extended to allow interactions between neighbouring receptor complexes arranged in a regular lattice according to the Ising model (the free energy of a receptor complex determined by the activity states of its immediate neighbours).</p> <p>Simulations run with different lattice sizes and geometries (hexagonal, square and trigonal) to gauge the effect of the coupling energy between neighbouring receptors on the signal-to-noise ratio and gain.</p> <p>Aspartate dose-response curves and receptor methylation patterns obtained for both zero and non-zero coupling energies.</p>
Mello and Tu (2003)	<p>A deterministic version of the stochastic model of Morton-Firth used to determine the full set of conditions under which the system achieves perfect adaptation.</p> <p>Each of these six conditions relaxed in turn to assess the magnitude of deviations from perfect adaptation, i.e., the regions of parameter space in which adaptation remains near-perfect.</p>
Rao et al. (2004)	<p>The first attempt at a model of the chemotaxis machinery in a different species: <i>Bacillus subtilis</i>.</p> <p>Experimental data and simulations show that, although there are two control loops in <i>B. subtilis</i> not present in <i>E. coli</i>, certain system design principles are shared in the two organisms.</p> <p>Proteins with homologues in both species generally do not function in the same way.</p> <p>Such diversity in conserved and non-conserved properties provides insight into the evolutionary processes at work.</p>
Lipkow et al. (2005)	<p>Stochastic model of CheY signalling using the Smoldyn program, simulating the diffusive movement of individual CheY molecules and their binding/reactive encounters with receptor complexes, CheZ and FliM.</p> <p>Uses an explicit, three-dimensional representation of the intracellular space, with excluded volumes mimicking the effects of crowding due to the nucleoid and large complexes.</p> <p>Simulations explore conditions for formation of CheYp gradients and response times of motors at different distances from the polar receptor cluster to attractant/repellent stimuli.</p>

Emonet et al. (2005) Multiscale model implemented in AgentCell, an agent-based program that relates stochastic intracellular processes to the behaviour of individual cells and bacterial populations. Cells represented as autonomous agents made up of chemotaxis proteins, motors and flagella that can move through a three-dimensional environment. Interactions of chemotaxis proteins in each agent implemented in StochSim as described above. Simulations reproduce the motion of single cells and the diffusion of populations both under unstimulating conditions and in chemoattractant gradients.

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