Decoupled Direct Method of Systematic Sensitivity Analysis: Application to Study of ERK1 Nuclear Translocation

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MATHEMATICAL modeling is increasingly being used to help explain biological and clinical observations. We describe a compartmental model developed to study signal transduction and other pathways. The ordinary differential equations (ODEs) governing time rate of change of species concentrations in the different compartments and intercompartmental species translocation rates (i.e., the "model problem") are solved by using the variable-step, variable-order, backward differentiation formula (BDF) method built into the packaged code LSODE [1]. Systematic sensitivity analysis generates the first-order sensitivity coefficients of species concentrations with respect to problem parameters, such as initial conditions and rate constants. We solve for these coefficients with the Decoupled Direct Method (DDM) [2, 3]. The ODEs for the model problem and sensitivity coefficients are solved in tandem: at each step, the solution to the model problem is first advanced, and then the sensitivity coefficients updated. Both solution procedures use the same step size and method order, which are automatically computed by the code and together minimize computational work, while maintaining user-prescribed accuracy. Although the DDM generates sensitivity coefficients of only the concentrations ("elementary sensitivities"), sensitivity coefficients of other quantities, such as of the temporal derivatives of concentrations, are easily derived ("derived sensitivities").

The accuracy of our solution method is first demonstrated by comparisons with published kinetics-only results (i.e., no sensitivity analysis) for the EGF/EGFR pathway under different conditions [4, 5]. We also demonstrate the accuracy of the sensitivity calculations by comparing our results with those in the literature for the same pathway [6]. We then apply our methods to study ERK1 nuclear translocation; in particular, ERK1 dimerization remains controversial, with some groups reporting that ERK1 dimerizes, while others do not observe it. To improve understanding of the mechanism of cytosol-to-nuclear translocation of ERK1, including the role of ERK1 dimerization, GFP-ERK1 constructs and real-time imaging were used to measure GFP intensity (and thus total ERK) in the two compartments as a function of time, after stimulation of the cell. In addition to the wild-type cell, the translocation behavior was measured in a mutant line with presumed inability to dimerize [7]. The rate of nuclear accumulation of ERK1 was much slower in the mutant than in the wild type, but the maximal relative amount was approximately the same in both cell types. The total (i.e., cellular) pERK concentration was also found to have much slower kinetics in the mutant cell than in the wild-type cell, although again the peak levels were of comparable magnitude.

To help understand these experimental observations and provide a plausible biological explanation, we used our computational models to study the cytosol-to-nucleus translocation process using a recently developed mechanism for the Ras/Raf/MEK/ERK cascade [8]. It does not include an ERK-dimer species, but does include reactions describing nucleus-cytosol translocation of ERK and pERK. Sensitivity analyses of the total concentration of pERK and its net rate of formation (i.e., time derivative) suggest that an explanation for the observed differences in nuclear translocation of ERK1 lies not only in the slower phosphorylation kinetics of ERK1 by pMEK, but also in the delayed release of pERK1 by pMEK in the mutant cell compared to the wild-type cell. Dramatically decreased phosphorylation of ERK1 by pMEK in other ERK1 mutants has also been observed [9].

Thus mathematical modeling has suggested biological experiments to elucidate the difference between the wild type and mutant cells; that is, the interactions between ERK1 and pMEK. The modeling has also provided a mechanism that does not need invocation of a dimer hypothesis. However, mathematical modeling cannot provide the proof that only well-planned biological experiments can, thus illustrating the synergism between systems biology and experimental biology.

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