Sensitivity Analysis for Uncertainty Quantification in Mathematical Models

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Abstract All mathematical models are approximate and their usefulness depends on our understanding the uncertainty inherent in the predictions. Uncertainties can affect the reliability of the results at every stage of computation; they may grow or even shrink as the solution of the model evolves. Often these inherent uncertainties cannot be made arbitrarily small by a more complex model or additional computation and we must understand how the uncertainty in the model parameters, the initial conditions, and the model itself, lead to uncertainties in the model predictions. This chapter is an introductory survey of sensitivity analysis and illustrates how to define the derivative of the model solution as a function of the model input and determine the relative importance of the model parameters on the model predictions.

1 Introduction and Overview

Sensitivity analysis (SA) can be used to quantify the effects of uncertainties on a model's input parameters and the subsequent effect on the model's output [2, 5–10, 13, 16, 19, 21–23, 27–30, 32]. That is, SA can determine how variability of the inputs causes variability in the outputs. The purpose of SA is to quantify this relationship through the ubiquitous derivative of the output as a function of the input. We provide an introductory survey of SA, how it's is done, what can go wrong, and apply SA to examples from epidemiology, illustrating how these tools can be used to improve mathematical models by quantitatively identifying key aspects that lead to strategies for reducing the spread of a disease.

1.1 Sensitivity Analysis: Forward and Adjoint Sensitivity

Consider a mathematical model consisting of user specified inputs, which are subsequently utilized by the model to create output solutions. Variations in the input parameters create variations in the output. The primary objective of SA is to

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precisely quantify the ratio of output perturbations with respect to the input perturbations. That is, SA provides an approach to determine which parameters have the most/least effect on the output solution. For example, if u denotes the output solution to a mathematical model and p denotes any of the input parameters, the primary objective of SA is to efficiently calculate $\partial u/\partial p$.

We introduce and apply the concepts and methodology of SA to three types of mathematical models:

- static problems
- dynamical systems
- optimization problems

Although static problems do not change in time, they can include complex relationships between parameters and the solution. As a typical example, consider solving a system of linear equations $\mathbf{Au} = \mathbf{b}$. SA can determine how the solution $\mathbf{u}$ depends on perturbations to the coefficients a_{ij} or the right-hand side terms b_i. Perturbations to these input parameters will directly affect the solution and raises the question: Which of these parameters has the most effect on the solution? To answer this question, we calculate the derivative expression $\partial u/\partial p$, where p represents any of the a_{ij} or b_i by introducing an auxiliary problem-the adjoint problem. This adjoint problem will allow us to efficiently find the desired derivative.

The same type of situation occurs for the common eigenvalue problem $\mathbf{Au} = \boldsymbol{\lambda}\mathbf{u}$ that arises, for example, in determining the reproductive number in epidemic models. Since the eigenstructure of this linear operator depends on the underlying parameter space, uncertainty in the a_{ij} produces uncertainty in the eigenvalues and eigenvectors of $\mathbf{A}$. SA is an approach that can define how λ or $\mathbf{u}$ will change if the elements of the matrix $\mathbf{A}$ change as measured by: $\partial\lambda/\partial a_{ij}$ and $\partial\mathbf{u}/\partial a_{ij}$. We will use the adjoint SA methodology to derive explicit formula for the derivatives of the eigenvalue and eigenvector. In epidemic models, the elements of $\mathbf{A}$ are often functions of the parameters, such as the infectivity or population size, in the underlying mathematical model and SA is used to determine how the eigenvalues change as a function of, say, a change in the transmission rate.

Epidemiological phenomena are often modeled by time dependent ordinary differential equations (ODEs), or if there is spatial, age, or other relational dependences, by partial differential equations (PDEs). If the time or spatial dependence is formulated on a lattice structure, then difference equations can be used as the mathematical model. Often the parameters or initial conditions (IC's) are not known exactly. Again, SA is an approach that can quantify how the uncertainty in input values is related to uncertainty in the model output $\mathbf{u} = \mathbf{u}(t)$. As in the static case, we will introduce an appropriate auxiliary problem, the adjoint problem. When chosen properly, the adjoint formation can reduce the computational complexity to answer targeted questions when the full SA is not needed, or is not computationally feasible.

1.2 Parameter Estimation

Parameter estimation is needed:

- when there is observational data with significant errors,
- when there are unknown or unspecified parameters, in the model that must be estimated (parameter estimation (PE)),
- to quantify the inevitable effects of uncertainty, in the observed data set and on the specification of parameter values, which ultimately leads to uncertainty in the model prediction (forward sensitivity analysis (FSA)), and
- to determine which regions in time or parameter space have the most effect on the model prediction (adjoint sensitivity analysis (ASA)).

Consider the graphical representation in Fig. 1 of the overall structure of the FSA problem, where **ODS** represents observational data set, **PS** denotes the parameter space, and **MP** represents the set of model predictions. Notice that the PS is partitioned into two disjoint sets; one containing those parameters for which we currently do not have specified values: $\{p_1, \ldots, p_k\}$, and the other set of parameters which do have assigned values $\{p_{k+1}, \ldots, p_{k+l}\}$. The application of a computational algorithm whereby one uses the incomplete ODS and obtains specific values for the unknown parameters can be viewed as the mapping $F : \text{ODS} \mapsto \{p_1, \ldots, p_k\}$. This is the objective of data assimilation. Once the unknown parameters are specified, the mathematical model can be evaluated providing the MP, that is, $G : \text{PS} \mapsto \text{MP}$.

Measurement errors in the ODS (shown as the dashed curves in Fig. 2) introduce uncertainties produce uncertainty in the PS, and hence uncertainty in the MP.

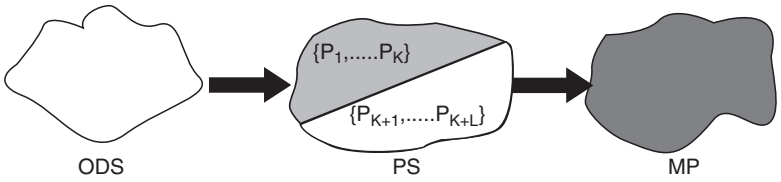

Fig. 1 Using the observational data set (ODS) to obtain values for unspecified parameters $\{p_1, \ldots, p_k\}$ in the parameter space (PS), which allows evaluation of the epidemiological model to obtain the model prediction (MP)

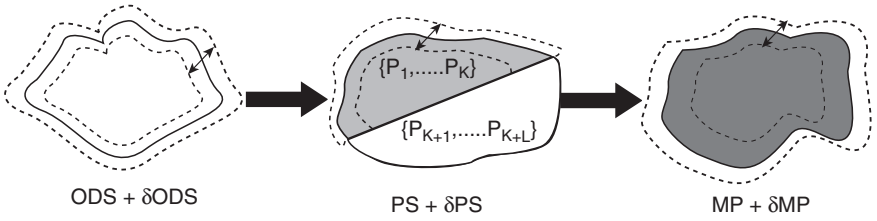

Fig. 2 Uncertainty in the ODS, (shown as *dashed curves*), produces uncertainty in the PS, which leads to uncertainty in the MP of the epidemiological model

We will describe local SA approaches to estimating the change in the solution resulting from small changes in nominal fixed values of the defining parameters. This introduction to SA will not discuss in detail the methodology of data assimilation, as applied to parameter estimation in epidemiology. However, we will provide the basic tools needed for parameter estimation. Furthermore, global SA (uncertainty quantification) [28] issues such as the sensitivity of bifurcation points, critical/degenerate points, extrema, variance-based methods such as Monte Carlo methods or the Fourier Amplitude Sensitivity Tests, Latin Hypercube or Fractional Factorial sampling, or Bayesian SA.

2 Sensitivity Analysis

2.1 Normalized Sensitivity Index

The fundamental objective of SA is to quantitatively estimate how uncertainty of inputs gives rise to uncertainties of the model outputs. In particular, we describe FSA and ASA for deterministic (non-stochastic) mathematical models.

FSA quantitatively determines how the output solution u, to our mathematical model, or some response function(al) $J(u)$, changes as small perturbations are made to a model parameter p, as is shown in Fig. 3. If the solution and functional are differentiable wrt. a parameter p, then in FSA we calculate the derivatives $\partial u/\partial p$ and $\partial J(u)/\partial p$ and define the *normalized sensitivity indexes* (SI):

$$S_{u_p} := \lim_{\delta p \to 0} \left(\frac{\delta u}{u}\right)\left(\frac{\delta p}{p}\right)^{-1} = \left(\frac{p}{u}\right)\frac{\partial u}{\partial p} \tag{1}$$

$$S_{J_p} := \lim_{\delta p \to 0} \frac{\delta J}{J}\left(\frac{\delta p}{p}\right)^{-1} = \left(\frac{J}{p}\right)\frac{\partial u}{\partial p}. \tag{2}$$

The normalized SI [13, 28–30] measure the relative change in the output $\delta u/u$ or $\delta J/J$, wrt. a small relative change to the input $\delta p/p$.

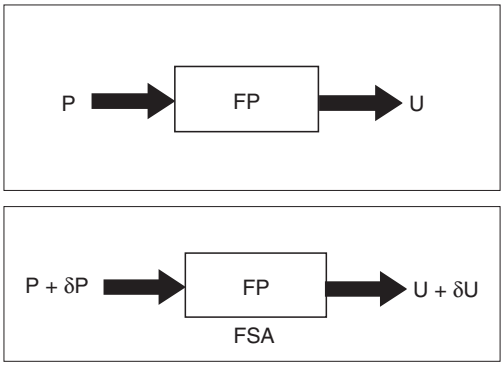

Fig. 3 The forward problem (FP-*top figure*) takes nominal input parameters p and produces the associated output solution u. Forward sensitivity analysis (FSA-*bottom figure*) introduces perturbations to the input parameters, via δp and quantifies the subsequent perturbations to the output solution via δu

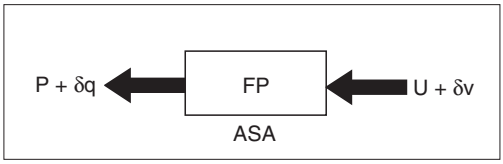

Fig. 4 Adjoint sensitivity analysis (ASA) introduces perturbations to the output solution, via δu and quantifies how these changes are related to perturbations in the input parameters via δp

One of the pitfalls in applying the results of SA is in not paying close attention to the relationships between the signs of S, u, δu, p, and δp. Often the output variable u is nonnegative, such as the infected population in an epidemic model and, without loss of generality, we will assume that the parameters and output variables in this article are all positive. When this is not the case, then the analysis must pay close attention to signs of the variables.

If the mathematical model is a dynamical system, then the SI can depend on time and the relative importance of the parameters can also depend on time. For example, for $t \leq t_c$, the parameter p_1 might have more affect on the solution than the parameter p_2, whereas for $t > t_c$ the roles of importance might reverse. This often occurs when comparing the relative importance of model parameters in early and late stages of an epidemic.

Whereas, for dynamical systems, FSA measures the future change in the solution caused by small changes in the parameters, ASA [12, 21–23] looks back in time, as shown in Fig. 4.

2.2 Motivation for Sensitivity Analysis

Consider the two species symbiotic population model [26] given by

$$\frac{du_1}{dt} = u_1(1 - u_1 - au_2) \tag{3}$$

$$\frac{du_2}{dt} = bu_2(1 - u_2 - cu_1), \tag{4}$$

where the parameters a, b, and c are nonnegative, ac is constant, and we are given the initial population of the two species as $u_1(0)$ and $u_2(0)$. For physical reasons, we require that the parameters satisfy the conditions $0 < a, c < 1$.

Some typical questions one might ask are

- Which of the parameters has the most influence on the value (not stability) of the equilibrium point(s)?
- Which of the parameters has the most influence on the stability/instability of the equilibrium points?
- Which of the parameters has the most influence on the time dependent solutions u_1 and u_2?

For more sophisticated models [1], numerous other relevant questions could easily come to mind. We will study this problem in more detail in the following sections.

3 Linear System of Equations and Eigenvalue Problem

3.1 Linear System of Equations: Symbiotic Population

For the two species symbiotic population model given above, let us determine which of the three parameters has the most influence on the value (not stability) of the equilibrium point(s) $(\bar{u}_1, \bar{u}_2)$ of Equations (3, 4). In other words, we would like to know how the solutions $(\bar{u}_1, \bar{u}_2)$ of the steady state system

$$\begin{aligned} \bar{u}_1(1 - \bar{u}_1 - a\bar{u}_2) &= 0 \\ b\bar{u}_2(1 - \bar{u}_2 - c\bar{u}_1) &= 0 \end{aligned}$$

are affected by changes to the two parameters a or c.

Solving this nonlinear system, we find the four equilibrium points

$$(\bar{u}_1, \bar{u}_2) = \left\{(0,0), (0,1), (1,0), \left(\frac{1-a}{1-ac}, \frac{1-c}{1-ac}\right)\right\}.$$

Notice that the extinct and single species equilibrium points (0, 0), (0, 1), and (1, 0) are independent of the a or c and therefore are unaffected by perturbations to these parameters. The two species equilibrium point however does depend on these parameters in which case we find the normalized relative sensitivity indices to be

$$\frac{a}{\bar{u}_1}\frac{\partial \bar{u}_1}{\partial a} = -\frac{a(1-c)}{(1-a)(1-ac)}, \qquad \frac{a}{\bar{u}_2}\frac{\partial \bar{u}_2}{\partial a} = \frac{ac}{1-ac},$$
$$\frac{c}{\bar{u}_1}\frac{\partial \bar{u}_1}{\partial c} = \frac{ac}{1-ac}, \qquad \text{and} \qquad \frac{c}{\bar{u}_2}\frac{\partial \bar{u}_2}{\partial c} = -\frac{c(1-a)}{(1-c)(1-ac)}.$$

Notice that the sensitivity of u_1 wrt. c is the same as it is for u_2 wrt. a.

The relative importance, as measured by the sensitivity indices, may be different in different regions of the parameter space. For this example, consider the sensitivity of u_1 wrt. a and u_2 wrt. c, where we want to know what the ordering is;

$$\begin{gathered} \frac{a}{\bar{u}_1}\frac{\partial \bar{u}_1}{\partial a} \boxed{?} \frac{c}{\bar{u}_2}\frac{\partial \bar{u}_1}{\partial c} \\ -\frac{a(1-c)}{(1-a)(1-ac)} \boxed{?} -\frac{c(1-a)}{(1-c)(1-ac)} \\ \frac{1-c}{\sqrt{c}} \boxed{?} \frac{1-a}{\sqrt{a}}. \end{gathered}$$

Here the symbol $\boxed{?}$ is an inequality symbol, such as $<$ or $>$. Since the function $f(x) := (1-x)/\sqrt{x}$, for $x \in (0, 1)$ is a strictly decreasing function, if $x_1 < x_2$, then

$f(x_1) > f(x_2)$. In other words, the relative importance, via the sensitivity indices, depends on whether $c > a$ or $c < a$.

Although we now have a methodology for determining the sensitivity of the equilibrium points, even more information can be gleaned by using SA for the evolution of the solution. In simpler examples the closed form solution is easily found and elementary calculus can be applied to find the associated sensitivity indices.

Let us restate and reformulate the problem of interest, that is to obtain the derivatives $\partial\bar{u}_1/\partial p$ and $\partial\bar{u}_2/\partial p$, where p represents any of the three parameters a, b or c. Even when the closed form solutions for the equilibrium points is not known, then we can directly construct the FSA by differentiating the equilibrium problem. The associated forward sensitivity equations (FSE) containing these derivatives are found by taking the partial derivatives $\partial/\partial p$ of both equilibrium equations, and applying the standard chain rule, to get the linear system

$$\mathbf{D}_{\mathbf{u}}\frac{\partial \mathbf{u}}{\partial p} = -\nabla_p F,$$

where, the notation we use will become apparent shortly,

$$\mathbf{D}_{\mathbf{u}} = \begin{pmatrix} 1 - 2\bar{u}_1 - a\bar{u}_2 & -a\bar{u}_1 \\ -bc\bar{u}_2 & b(1 - 2\bar{u}_2 - c\bar{u}_1) \end{pmatrix}, \quad \frac{\partial \mathbf{u}}{\partial p} = \begin{pmatrix} \dfrac{\partial \bar{u}_1}{\partial p} \\ \dfrac{\partial \bar{u}_2}{\partial p} \end{pmatrix},$$

$$\nabla_p F = \begin{pmatrix} -\bar{u}_1\bar{u}_2\dfrac{\partial a}{\partial p} \\ -\bar{u}_1\bar{u}_2\dfrac{\partial c}{\partial p} \end{pmatrix}.$$

One could calculate $\mathbf{D}_{\mathbf{u}}^{-1}$ directly, however for large systems of equations this procedure is both analytically difficult or computationally expensive. Direct inversion of the linear operator should always be avoided, except in very small systems. Instead for large systems, we obtain $\mathbf{D}_{\mathbf{u}}^{-1}\nabla_p F$ by introducing an auxiliary problem called the adjoint problem.

Before describing the adjoint problem, we make the important observation that the system of equations defining the derivative $d\mathbf{u}/dp$ is *always* a linear system, even though the original system was nonlinear. This particular example suggests that although the equilibrium point(s) could be solutions to nonlinear equations, the FSE's are linear in the derivative terms. To see this is true in general, consider the 2-D system

$$\frac{du_1}{dt} = f_1(u_1, u_2; p)$$
$$\frac{du_2}{dt} = f_2(u_1, u_2; p)$$

where f_1 and f_2 are differentiable in u_1, u_2 and p. Since the equilibrium points are solutions of the nonlinear system

$$f_1(\bar{u}_1, \bar{u}_2; p) = 0$$
$$f_2(\bar{u}_1, \bar{u}_2; p) = 0$$

then the associated FSE's is the linear system

$$\mathbf{D}_{\mathrm{u}} \frac{\partial \mathbf{u}}{\partial p} = -\nabla_p F, \tag{5}$$

where

$$\mathbf{D}_{\mathbf{u}} = \begin{pmatrix} \dfrac{\partial f_1}{\partial \bar{u}_1} & \dfrac{\partial f_1}{\partial \bar{u}_2} \\ \dfrac{\partial f_2}{\partial \bar{u}_1} & \dfrac{\partial f_2}{\partial \bar{u}_2} \end{pmatrix}, \quad \frac{\partial \mathbf{u}}{\partial p} = \begin{pmatrix} \dfrac{\partial \bar{u}_1}{\partial p} \\ \dfrac{\partial \bar{u}_2}{\partial p} \end{pmatrix}, \quad \nabla_p F = \begin{pmatrix} \dfrac{\partial f_1}{\partial p} \\ \dfrac{\partial f_2}{\partial p}. \end{pmatrix}.$$

The notation chosen is suggestive: $\mathbf{D_u}$ denotes the Jacobian wrt. the variables $\mathbf{u}$ and $\nabla_p F$ denotes the gradient wrt. the parameters $\mathbf{p}$.

Thus, the FSE for the equilibrium solutions of the IVP can be written in the general form

$$\mathbf{A}\mathbf{w} = \mathbf{b}, \tag{6}$$

where $\mathbf{A}$ is a real $N \times N$ nonsymmetric and nonsingular matrix, which in this example is the Jacobian matrix. Let p denote any of the parameters a_{ij} or b_i and assume that for the specified values of p, the forward solution $\mathbf{w}$ is a differentiable function of the parameters and is sufficiently far away from any singularities in the parameter space, then the FSE are given by

$$\mathbf{A}\frac{\partial \mathbf{w}}{\partial p} = \frac{\partial \mathbf{b}}{\partial p} - \frac{\partial \mathbf{A}}{\partial p}\mathbf{w}. \tag{7}$$

Since perturbations to the parameter p produces perturbations in the forward solution $\mathbf{w}$, FSA requires the calculation of the derivative $\partial \mathbf{w}/\partial p$. This FSE equation could be solved by premultiplying by the matrix inverse $\mathbf{A}^{-1}$, however, for larger systems, this procedure is computationally expensive, often numerically unstable, and should be avoided if at all possible.

The ASA accomplishes the same goal, while avoiding computing $\mathbf{A}^{-1}$, by introducing an auxiliary problem which isolates how the solution depends on the parameters; that is, $\partial \mathbf{w}/\partial p$. This is accomplished by defining an appropriate inner product and cleverly choosing conditions so as to isolate the desired quantity. For

this simple case, we use the usual vector inner product for standard Euclidean space and premultiply the FSE by some, as of yet unspecified, nontrivial vector $\mathbf{v}^T$

$$\mathbf{v}^T \mathbf{A} \frac{\partial \mathbf{w}}{\partial p} = \mathbf{v}^T \left(\frac{\partial \mathbf{b}}{\partial p} - \frac{\partial \mathbf{A}}{\partial p} \mathbf{w} \right). \tag{8}$$

Now consider the $1 \times N$ vector $\mathbf{c}^T := \mathbf{v}^T \mathbf{A}$, or written as the associated adjoint problem

$$\mathbf{A}^T \mathbf{v} = \mathbf{c}. \tag{9}$$

Since we wish to isolate the derivative term $\partial \mathbf{w}/\partial p$, choose N forcing vectors of the form $\mathbf{c_i}^T = \big(0 \cdots 0\ 1\ 0 \cdots 0\big)$, where the 1 is located in the ith column. This forces the product $\mathbf{v}^T \mathbf{A}$ to project out the desired components $\partial w_i/\partial p$, for $i = 1, \ldots, N$, in which case

$$\frac{\partial w_i}{\partial p} = \mathbf{v_i}^T \left(\frac{\partial \mathbf{b}}{\partial p} - \frac{\partial \mathbf{A}}{\partial p} \mathbf{w} \right). \tag{10}$$

This particular choice for the adjoint problem leads to an intimate relationship between the inverse matrix $\mathbf{A}^{-1}$ and the matrix of adjoint vectors $\mathbf{V} := \big(\mathbf{v_1}\ \mathbf{v_2} \cdots \mathbf{v_N}\big)$, namely $\mathbf{V}^T = \mathbf{A}^{-1}$. The relationships between the forward and adjoint problems and sensitivity equations, in this example, shown in Fig. 5, illustrates connections between the forward and adjoint problem.

3.2 Stability of the Equilibrium Solution: The Eigenvalue Problem

The stability of the equilibrium solution of (3) and (4) depends upon the eigenvalues of the Jacobian of the linearized system at the equilibrium. These eigenvalues are functions of the parameters p. Therefore, we can use sensitivity analysis to

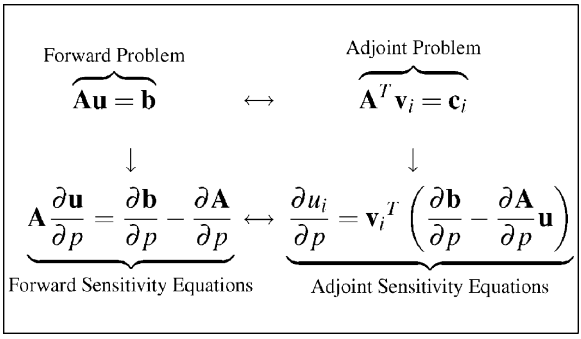

Fig. 5 The relationships between the forward sensitivity and associated adjoint problems creates a self-consistant framework for sensitivity analysis

determine how the stability of an equilibrium point is affected by changes to the parameters. The eigenvalues λ of the Jacobian

$$A = \begin{pmatrix} 1 - 2\bar{u}_1 - a\bar{u}_2 & -a\bar{u}_1 \\ -bc\bar{u}_2 & b\,(1 - 2\bar{u}_2 - c\bar{u}_1) \end{pmatrix} \tag{11}$$

could be found by constructing the characteristic polynomial and solving the associated characteristic equation

$$p(\lambda) = \lambda^2 - (1 - 2\bar{u}_1 - a\bar{u}_2 + b(1 - c\bar{u}_1 - 2\bar{u}_2)\,\lambda - abc\bar{u}_1\bar{u}_2 \quad \text{and} \quad p(\lambda) = 0.$$

For this simple problem, the eigenvalues can be explicitly found, and subsequently the derivatives $\partial\lambda/\partial p$ can be calculated. However, as the system of differential equations increases, so does the degree of the associated characteristic polynomial and this approach becomes impracticable. The roots of high degree polynomials cannot be defined analytically, and the numerical methods for finding these roots often suffer from numerical instabilities.

As was done in the previous example of finding the sensitivity of a linear system of equations, we proceed to find the sensitivity of the right eigenvalue problem[1]

$$\mathbf{A}\mathbf{u} = \lambda\mathbf{u} \tag{12}$$

where $\mathbf{A}$ is an $N \times N$ nonsymmetric matrix with distinct eigenvalues and an associated complete, nonorthonormal set of eigenvectors, which span $\mathbb{R}^N$. This particular example will shed light on a significant inherent limitation of ASE that is rarely discussed, much less emphasized.

Since the eigenvalues λ and the eigenvectors $\mathbf{u}$ depend on the coefficients a_{ij}, differentiate the right eigenvalue problem to get the FSE

$$\mathbf{A}\frac{\partial \mathbf{u}}{\partial a_{ij}} + \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{u} = \lambda\frac{\partial \mathbf{u}}{\partial a_{ij}} + \frac{\partial \lambda}{\partial a_{ij}}\mathbf{u}. \tag{13}$$

The difficulty that arises in this example is that there are two unknown derivatives of interest, the derivative of the eigenvalues $\partial\lambda/\partial a_{ij}$ and the derivative of the eigenvectors $\partial\mathbf{u}/\partial a_{ij}$. The purpose of the adjoint methodology is to produce one, and only one, additional auxiliary problem. That is, a single associated adjoint problem can only be used to find the derivative of the eigenvalues or the derivative of the eigenvectors, but not both simultaneously. As we will show, using the adjoint problem to find $\partial\lambda/\partial a_{ij}$ precludes the ability to find $\partial\mathbf{u}/\partial a_{ij}$, unless additional information is provided.

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[1] As we will see shortly, the associated left eigenvalue problem is the adjoint problem for (12), namely $\mathbf{A}^T\mathbf{v} = \lambda\mathbf{v}$.

Let $\mathbf{v}$ be some nonzero, as yet unspecified, vector and take the inner product with the FSE (13) to get

$$\frac{\partial \lambda}{\partial a_{ij}} \langle \mathbf{u}, \mathbf{v} \rangle = \left\langle \frac{\partial \mathbf{A}}{\partial a_{ij}} \mathbf{u}, \mathbf{v} \right\rangle + \left\langle (\mathbf{A} - \lambda \mathbf{I}) \frac{\partial \mathbf{u}}{\partial a_{ij}}, \mathbf{v} \right\rangle. \tag{14}$$

Because $(\mathbf{A} - \lambda \mathbf{I})^T = \mathbf{A}^T - \lambda \mathbf{I}$, we can use the Lagrange identity for matrices, under the usual inner product, to get

$$\left\langle (\mathbf{A} - \lambda \mathbf{I}) \frac{\partial \mathbf{u}}{\partial a_{ij}}, \mathbf{v} \right\rangle = \left\langle \frac{\partial \mathbf{u}}{\partial a_{ij}}, \left(\mathbf{A}^T - \lambda \mathbf{I}\right) \mathbf{v} \right\rangle.$$

Now annihilate the second inner product by forcing the adjoint condition

$$\mathbf{A}^T \mathbf{v} = \lambda \mathbf{v}, \tag{15}$$

which is known as the left eigenvalue problem. For the original eigenvalue problem, the left eigenvalue problem is the associated adjoint problem. (For more details, see [18, 32].)

The properties of the left and right eigenvalue problems include:

- If the right eigenvalue problem has a solution, then the left eigenvalue also has a solution.
- The right and left eigenvectors $\mathbf{u}$ and $\mathbf{v}$ are distinct, for a specified eigenvalue λ.
- The right eigenvectors $\mathbf{u}^{(k)} = \left(u_1{}^{(k)}\ u_2{}^{(k)} \cdots u_N{}^{(k)}\right)^T$ and left eigenvectors $\mathbf{v}^{(l)} = \left(v_1{}^{(l)}\ v_2{}^{(l)} \cdots v_N{}^{(l)}\right)^T$ are orthogonal for $k \neq l$ and $\left\langle \mathbf{u}^{(k)}, \mathbf{v}^{(k)} \right\rangle \neq 0$ for $k = l$.
- Using the previous result, the right and left eigenvectors can be normalized, i.e., $\left\langle \mathbf{u}^{(k)}, \mathbf{v}^{(k)} \right\rangle = 1$.

Using the left eigenvalue problem (adjoint problem), Equation (14) reduces to

$$\frac{\partial \lambda}{\partial a_{ij}} \langle \mathbf{u}, \mathbf{v} \rangle = v_i\, u_j.$$

Since the right and left eigenvectors are normalized, the explicit expression for the derivative of the eigenvalue wrt. the coefficients a_{ij} is

$$\frac{\partial \lambda}{\partial a_{ij}} = v_i\, u_j. \tag{16}$$

To find an explicit expression for $\partial \mathbf{u}/\partial a_{ij}$, we must introduce additional information. The reason for this diversion is that no new information can be gleened about $\partial \mathbf{u}/\partial a_{ij}$ from the adjoint problem. The key to making further progress is to recall that we have assumed that the $N \times N$ matrix $\mathbf{A}$ has N distinct eigenvalues, in which case there exists a complete set of N eigenvectors. We now make use of the

fact that any vector in $\mathbb{C}^N$ can be expressed as a linear combination of the spanning eigenvectors. Since $\partial \mathbf{u}/\partial a_{ij}$ is an $N \times 1$ vector, we can write this derivative as a linear combination of the eigenvectors.

It will be helpful to introduce some additional notation describing the right and left eigenvector matrices $\mathbf{U}$ and $\mathbf{V}$, whose columns are the individual eigenvectors $\mathbf{u}^{(k)}$ and $\mathbf{v}^{(k)}$ respectively, and let Λ be the diagonal matrix of eigenvalues λ_k, that is

$$\mathbf{U} := \left(\mathbf{u}^{(1)}\ \mathbf{u}^{(2)}\ \cdots\ \mathbf{u}^{(N)}\right), \quad \mathbf{V} := \left(\mathbf{v}^{(1)}\ \mathbf{v}^{(2)}\ \cdots\ \mathbf{v}^{(N)}\right) \quad \text{and} \quad \Lambda := \begin{pmatrix} \lambda_1 & & & \mathbf{0} \\ & \lambda_2 & & \\ & & \ddots & \\ \mathbf{0} & & & \lambda_N \end{pmatrix}.$$

Using this notation, the right and left eigenvalue problems can be written as

$$\mathbf{A}\mathbf{U} = \mathbf{U}\Lambda \qquad \text{and} \qquad \mathbf{A}^T\mathbf{V} = \mathbf{V}\Lambda. \tag{17}$$

Earlier we forced the right and left eigenvectors to be normalized, and therefore the matrix of eigenvectors satisfy the identity

$$\mathbf{V}^T\mathbf{U} = \mathbf{I}. \tag{18}$$

The derivative of the matrix of eigenvectors can written as a linear combination of the eigenspace;

$$\frac{\partial \mathbf{U}}{\partial a_{ij}} = \mathbf{U}\mathbf{C}\,. \tag{19}$$

This equation defines the coefficient matrix

$$\mathbf{C} := \begin{pmatrix} {c_1}^{(1)} & {c_1}^{(2)} & {c_1}^{(3)} & \cdots & {c_1}^{(N)} \\ {c_2}^{(1)} & {c_2}^{(2)} & {c_2}^{(3)} & \cdots & {c_2}^{(N)} \\ \vdots & & \vdots & & \vdots \\ {c_N}^{(1)} & {c_N}^{(2)} & {c_N}^{(3)} & \cdots & {c_N}^{(N)} \end{pmatrix}, \tag{20}$$

where for a fixed eigenvector $\mathbf{u}^{(k)}$, the derivative can be expanded as the sum

$$\frac{\partial \mathbf{u}^{(k)}}{\partial a_{ij}} = {c_1}^{(k)}\mathbf{u}^{(1)} + \cdots + {c_k}^{(k)}\mathbf{u}^{(k)} + \cdots {c_N}^{(k)}\mathbf{u}^{(N)}. \tag{21}$$

We now describe how to define the coefficients ${c_l}^{(m)}$.

Differentiating the right eigenvector matrix Equation (17) gives

$$\mathbf{A}\frac{\partial \mathbf{U}}{\partial a_{ij}} + \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{U} = \mathbf{U}\frac{\partial \Lambda}{\partial a_{ij}} + \frac{\partial \mathbf{U}}{\partial a_{ij}}\Lambda. \tag{22}$$

Using Equation (17) and (19) and rearranging we get

$$\mathbf{U}\,[\Lambda, \mathbf{C}] = \mathbf{U}\frac{\partial \Lambda}{\partial a_{ij}} - \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{U}, \tag{23}$$

where $[\cdot,]$ denotes the commutator bracket $[\Lambda, \mathbf{C}] := \Lambda\mathbf{C} - \mathbf{C}\Lambda$.

Next, premultiply by the left eigenvector matrix and use the normalization condition, this equation reduces to

$$[\Lambda, \mathbf{C}] = \frac{\partial \Lambda}{\partial a_{ij}} - \mathbf{V}^T \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{U}. \tag{24}$$

Expanding the commutator bracket we find that

$$[\Lambda, \mathbf{C}] = \begin{pmatrix} 0 & c_1{}^{(2)}(\lambda_1 - \lambda_2) & c_1{}^{(3)}(\lambda_1 - \lambda_3) & \cdots c_1{}^{(N)}(\lambda_1 - \lambda_N) \\ c_2{}^{(1)}(\lambda_2 - \lambda_1) & 0 & c_2{}^{(3)}(\lambda_2 - \lambda_3) & \cdots c_2{}^{(N)}(\lambda_2 - \lambda_N) \\ c_3{}^{(1)}(\lambda_3 - \lambda_1) & c_3{}^{(2)}(\lambda_3 - \lambda_2) & 0 & \cdots c_3{}^{(N)}(\lambda_3 - \lambda_N) \\ \vdots & & & \ddots \quad \vdots \\ c_N{}^{(1)}(\lambda_N - \lambda_1) & c_N{}^{(2)}(\lambda_N - \lambda_2) & c_N{}^{(3)}(\lambda_N - \lambda_3) & \cdots \quad 0 \end{pmatrix} \tag{25}$$

Since the right side of Equation (24) is known, and because we assumed that the eigenvalues are distinct, we can solve for the off-diagonal coefficients

$$c_l{}^{(m)} = -\frac{1}{\lambda_l - \lambda_m}\left[\mathbf{V}^T \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{U}\right]_{lm} \quad \text{for} \quad l \neq m. \tag{26}$$

The next task is to find the values of the diagonal coefficients. Once again, we make use of the fact that the eigenvectors form a basis for $\mathbb{C}^N$. To solve for the scalar diagonal coefficients $c_k{}^{(k)}$ in (21), we first transform this vector equation to a scalar equation by normalizing the right eigenvectors. That is, we force the condition $\langle \mathbf{u}^k, \mathbf{u}^k \rangle = 1$. Next, we fix the indexes i, j and differentiate this normalization condition to get

$$\mathbf{u}^{kT}\frac{\partial \mathbf{u}^k}{\partial a_{ij}} + \frac{\partial \mathbf{u}^{kT}}{\partial a_{ij}}\mathbf{u}^k = 0.$$

Because

$$\frac{\partial \mathbf{u}^{kT}}{\partial a_{ij}}\mathbf{u}^k = \mathbf{u}^{kT}\frac{\partial \mathbf{u}^k}{\partial a_{ij}},$$

it follows that $\mathbf{u}^k$ and $\partial \mathbf{u}^k / \partial a_{ij}$ are orthogonal, in which case we obtain the N equations

$$\left\langle \frac{\partial \mathbf{u}^k}{\partial a_{ij}}, \mathbf{u}^k \right\rangle = 0, \qquad \text{for} \quad k = 1, \ldots N. \tag{27}$$

Next premultiply, the summed version of the derivative of the eigenvector (21), by $\mathbf{u}^{(k)}$ to get

$$c_1{}^{(k)} \langle \mathbf{u}^{(1)}, \mathbf{u}^{(k)} \rangle + \cdots + c_k{}^{(k)} \langle \mathbf{u}^{(k)}, \mathbf{u}^{(k)} \rangle + \cdots c_N{}^{(k)} \langle \mathbf{u}^{(N)}, \mathbf{u}^{(k)} \rangle = 0.$$

Since the individual eigenvectors have been normalized, we can solve for the diagonal coefficients in terms of the known off diagonal coefficients:

$$c_k{}^{(k)} = - \sum_{\substack{i=1 \\ i \neq k}}^{N} c_i{}^{(k)} \langle \mathbf{u}^{(i)}, \mathbf{u}^{(k)} \rangle. \tag{28}$$

4 Dimensionality Reduction

When considering a mathematical model where some of the variables may be redundant, one would like to be able to identify, with confidence, those variables that can be safely eliminated without affecting the validity of the model. To not inadvertently eliminate significant variables, one must identify *groups* of variables that are highly correlated. In essence, one is trying to identify those aspects of the model that are comprised of strongly interacting mechanisms. A problem arises when one uses data, which contain errors or noise, to estimate the correlation between these variables and use these estimates to determine which variables can be safely eliminated. Thus, uncertainty in the data can create uncertainty in the correlation estimates and ultimately in the reduced model.

For example, consider an imaginary disease for which a specific blood test can, with certainty, identify whether the patient has or does not have this disease. Now suppose that there exists a medication whose sole purpose is to treat this particular disease. When constructing a model of this scenario, the number of prescriptions for this medication and the positive blood test results are highly correlated. Assuming that the examining physician always prescribes this medication the correlation would in fact be 1.0. The information contained in these two data sets are redundant. Either the number of positive blood test results or the number of prescriptions provides sufficient information about the number of positively diagnosed infections. Taking a geometric perspective of this scenario, since the two data sets are so highly correlated, a projection from a 2-dimensional parameter space to a 1-dimensional space would be appropriate.

Now consider the more realistic scenario where public health officials are monitoring a seasonal outbreak of a disease. Syndromic surveillance or biosurveillance data of clinical symptoms such as fever, number of hospital admissions, over-the-counter medication consumption, respiratory complaints, school or work

absences, etc., while readily available, does not directly provide accurate numerical quantification of the size of the outbreak. Furthermore, "noise" in the data causes inaccuracy of any specific numerical assessments or predictions. Additionally, symptoms such as fever and respiratory complaints have different levels of correlation for different diseases, and therefore difficulties arise in determining which factors are redundant and which factors are essential to the model. In other words, it would be desirable to identify the highly correlated variables, in which case we could reduce the dimension of the data, without significantly degrading the validity of the model, and minimize the effects of noise.

4.1 Principal Component Analysis

Principal component analysis (PCA) is a powerful method of modern data analysis that provides a systematic way to reduce the dimension of a complex data set to a lower dimension, and oftentimes reveals hidden simplified structures that would otherwise go unnoticed.

Consider an $M \times N$ matrix of data measurements $\mathbf{A}$ with M data types and N observations of each data type. Each $M \times 1$ column of $\mathbf{A}$ represents the measurement of the data types at some time t for which there are N time samples. Since any $M \times 1$ vector lies in an M-dimensional vector space, then there exists an M-dimensional orthonormal basis that spans the vector space. The goal of PCA is to transform the noisy, and possibly redundant data, set to a lower dimensional orthonormal basis. The desired result is that this new basis will effectively and successively filter out the noisy data and reveal hidden structures among the data types.

The way this is accomplished is based on the idea of noise, rotation, and covariance. When performing measurements, the problem of quantifying the effect of noise has on the data set is often defined by the signal-to-noise ratio (SNR) and is defined as the ratio of variances

$$SNR := \frac{{\sigma^2}_{\text{Signal}}}{{\sigma^2}_{\text{Noise}}}. \tag{29}$$

If the SNR is large, then the signal/measurements are accurate; whereas, if SNR is small, then the data is significantly contaminated by noise. Since one of the goals of PCA is transform the data to a basis that minimizes the effect of noise, PCA increases the SNR by maximizing the signal variance. Secondly, data identified having high covariance is used to guide in reducing the dimension of the data set.

4.2 Singular Value Decomposition (SVD)

Let $\mathbf{A}$ be a real $M \times N$ matrix and let r denote the rank of $\mathbf{A}$. Recall some essential geometric properties of matrices:

1. The matrix $\mathbf{A}$ maps the unit sphere in $\mathbb{R}^N$ and into a hyperellipsoid in $\mathbb{R}^M$.

2. The directions of the hyper-axes of the ellipsoid are denoted by the orthogonal basis $\{\mathbf{u}^{(k)}\}$, for $k = 1, \ldots M$ (singular vectors).
3. The stretching/compression factors, (singular values) are denoted by $\{\sigma_k\}$.
4. The vectors $\sigma_k \mathbf{u}^{(k)}$ define the principal semi-axes of the hyperellipsoid.

The SVD defines the particular factorization of $\mathbf{A}$, in terms of the above geometric properties, as

$$\mathbf{A} = \mathbf{U} \underset{\sim}{\Sigma} \mathbf{V}^T \tag{30}$$

where

- the $M \times M$ matrix $\mathbf{U}$ is unitary (i.e., $\mathbf{U}^T\mathbf{U} = \mathbf{I}$, where T denotes transpose and $\mathbf{I}$ is the $M \times M$ identity matrix) and the columns $\mathbf{u}^{(k)}$ form an orthogonal basis for $\mathbb{R}^M$,
- similarly, the $N \times N$ matrix $\mathbf{V}$ is also unitary and the column $\mathbf{v}^{(k)}$ form an orthogonal basis for $\mathbb{R}^N$, and
- the $M \times N$ diagonal matrix $\underset{\sim}{\Sigma}$ is

$$\underset{\sim}{\Sigma} = \begin{pmatrix} \sigma_1 & & & & \mathbf{0} \\ & \ddots & & & \\ & & \sigma_r & & \\ & & & 0 & \\ & & & & \ddots \\ \mathbf{0} & & & & 0 \end{pmatrix}, \tag{31}$$

where the singular values are ordered as $\sigma_1 > \sigma_2 > \cdots > \sigma_r > \sigma_{r+1} = \cdots = \sigma_p = 0$ and $p := \min(M, N)$.

The way to find the M columns $\mathbf{u}$ of $\mathbf{U}$, and the N columns $\mathbf{v}$ of $\mathbf{V}$, where

$$\mathbf{U} := \left(\mathbf{u}^{(1)}\ \mathbf{u}^{(2)} \cdots \mathbf{u}^{(M)}\right), \quad \mathbf{V} := \left(\mathbf{v}^{(1)}\ \mathbf{v}^{(2)} \cdots \mathbf{v}^{(N)}\right)$$

is to solve the left and right eigenvalue problems

$$\mathbf{A}\mathbf{v} = \sigma\mathbf{u}, \qquad \text{and} \qquad \mathbf{A}^T\mathbf{u} = \sigma\mathbf{v}. \tag{32}$$

Note that because the columns of U and V are the eigenvectors of AA^T, the norms of these matrix vector products are the same as the norms of the eigenvectors.

4.3 Sensitivity of SVD

Because the singular values σ and the singular vectors $\mathbf{u}$ and $\mathbf{v}$ depend on the coefficients a_{ij}, we can differentiate the left and right eigenvalue problems (32) to get the FSE

$$\mathbf{A}\frac{\partial \mathbf{v}}{\partial a_{ij}} + \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{v} = \sigma \frac{\partial \mathbf{u}}{\partial a_{ij}} + \frac{\partial \sigma}{\partial a_{ij}}\mathbf{u}, \tag{33}$$

$$\mathbf{A}^T\frac{\partial \mathbf{u}}{\partial a_{ij}} + \frac{\partial \mathbf{A}^T}{\partial a_{ij}}\mathbf{u} = \sigma \frac{\partial \mathbf{v}}{\partial a_{ij}} + \frac{\partial \sigma}{\partial a_{ij}}\mathbf{v}. \tag{34}$$

Because the matrices $\mathbf{U}$ and $\mathbf{V}$ are unitary, the associated singular vectors $\mathbf{u}$ and $\mathbf{v}$ are normalized, i.e.,

$$\langle \mathbf{u}, \mathbf{u} \rangle = \langle \mathbf{v}, \mathbf{v} \rangle = 1.$$

Using this result we find the useful orthogonality condition

$$\mathbf{u}^T\frac{\partial \mathbf{u}}{\partial a_{ij}} = \mathbf{v}^T\frac{\partial \mathbf{v}}{\partial a_{ij}} = 0. \tag{35}$$

Premultiply the left FSE given in (33) by $\mathbf{u}^T$ and, using the orthogonality and normalizing conditions, the FSE reduces to

$$\mathbf{u}^T\mathbf{A}\frac{\partial \mathbf{v}}{\partial a_{ij}} + \mathbf{u}^T\frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{v} = \frac{\partial \sigma}{\partial a_{ij}}. \tag{36}$$

The right eigenvalue problem, rewritten as $\mathbf{u}^T\mathbf{A} = \sigma\mathbf{v}^T$, is used with the orthogonality condition (35) to eliminate the first term in (36) to give:

$$\begin{aligned}\frac{\partial \sigma}{\partial a_{ij}} &= \mathbf{u}^T\frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{v} \\ &= u_i v_j.\end{aligned} \tag{37}$$

for $i = 1, \ldots, M$ and $j = 1, \ldots, N$

Now using the matrix notation, the left and right eigenvalue problems can be written in matrix form

$$\mathbf{A}\,\mathbf{V} = \mathbf{U}\,\underset{\sim}{\Sigma} \qquad \text{and} \qquad \mathbf{A}^T\,\mathbf{U} = \mathbf{V}\,\underset{\sim}{\Sigma}^T. \tag{38}$$

Since the derivative of the singular vector is in $\mathbb{R}^M$, it can be written as a linear combination of the singular vectors, define the coefficient matrix as

$$\mathbf{C} := \begin{pmatrix} {c_1}^{(1)} & {c_1}^{(2)} & {c_1}^{(3)} & \cdots & {c_1}^{(M)} \\ {c_2}^{(1)} & {c_2}^{(2)} & {c_2}^{(3)} & \cdots & {c_2}^{(M)} \\ \vdots & & \vdots & & \vdots \\ {c_M}^{(1)} & {c_M}^{(2)} & {c_M}^{(3)} & \cdots & {c_M}^{(M)} \end{pmatrix}, \tag{39}$$

so that the derivative of the eigenvector matrix can be written as

$$\frac{\partial \mathbf{U}}{\partial a_{ij}} = \mathbf{U}\mathbf{C}. \tag{40}$$

Differentiating the right eigenvector matrix equation gives

$$\mathbf{A}^T \frac{\partial \mathbf{U}}{\partial a_{ij}} + \frac{\partial \mathbf{A}^T}{\partial a_{ij}}\mathbf{U} = \mathbf{V}\frac{\partial \underset{\sim}{\Sigma}^T}{\partial a_{ij}} + \frac{\partial \mathbf{V}}{\partial a_{ij}}\underset{\sim}{\Sigma}^T. \tag{41}$$

Using (40), we get

$$\mathbf{A}^T\mathbf{U}\mathbf{C} - \frac{\partial \mathbf{V}}{\partial a_{ij}}\underset{\sim}{\Sigma}^T = \mathbf{V}\frac{\partial \underset{\sim}{\Sigma}^T}{\partial a_{ij}} - \frac{\partial \mathbf{A}^T}{\partial a_{ij}}\mathbf{U}. \tag{42}$$

To replace the derivative $\partial \mathbf{V}/\partial a_{ij}$ in terms of the product $\mathbf{UC}$, differentiate the left eigenvalue problem to obtain

$$\mathbf{A}\frac{\partial \mathbf{V}}{\partial a_{ij}} = \mathbf{U}\frac{\partial \underset{\sim}{\Sigma}}{\partial a_{ij}} + \mathbf{U}\mathbf{C}\underset{\sim}{\Sigma} - \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{V}.$$

Next, premultiply Equation (42) by matrix $\mathbf{A}$, and using this result gives

$$\begin{aligned}
\mathbf{A}\mathbf{A}^T\mathbf{U}\mathbf{C} - \mathbf{A}\frac{\partial \mathbf{V}}{\partial a_{ij}}\underset{\sim}{\Sigma}^T &= \mathbf{A}\mathbf{V}\frac{\partial \underset{\sim}{\Sigma}^T}{\partial a_{ij}} - \mathbf{A}\frac{\partial \mathbf{A}^T}{\partial a_{ij}}\mathbf{U} \\
\mathbf{A}\mathbf{A}^T\mathbf{U}\mathbf{C} - \left(\mathbf{U}\frac{\partial \underset{\sim}{\Sigma}}{\partial a_{ij}} + \mathbf{U}\mathbf{C}\underset{\sim}{\Sigma} - \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{V}\right)\underset{\sim}{\Sigma}^T &= \mathbf{A}\mathbf{V}\frac{\partial \underset{\sim}{\Sigma}^T}{\partial a_{ij}} - \mathbf{A}\frac{\partial \mathbf{A}^T}{\partial a_{ij}}\mathbf{U}.
\end{aligned}$$

Rearranging so as to isolate the expressions containing $\mathbf{UC}$, on the left side of the equation, we get

$$\mathbf{A}\mathbf{A}^T\mathbf{U}\mathbf{C} - \mathbf{U}\mathbf{C}\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T = \mathbf{A}\mathbf{V}\frac{\partial \underset{\sim}{\Sigma}^T}{\partial a_{ij}} - \mathbf{A}\frac{\partial \mathbf{A}^T}{\partial a_{ij}}\mathbf{U} + \mathbf{U}\frac{\partial \underset{\sim}{\Sigma}}{\partial a_{ij}}\underset{\sim}{\Sigma}^T - \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{V}\underset{\sim}{\Sigma}^T.$$

Consider the pair of expressions on the left side of this equation

$$\begin{aligned}
\mathbf{A}\mathbf{A}^T\mathbf{U}\mathbf{C} - \mathbf{U}\mathbf{C}\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T &= \mathbf{A}\mathbf{V}\underset{\sim}{\Sigma}^T\mathbf{C} - \mathbf{U}\mathbf{C}\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T \\
&= \mathbf{U}\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T\mathbf{C} - \mathbf{U}\mathbf{C}\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T \\
&= \mathbf{U}\left[\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T, \mathbf{C}\right],
\end{aligned}$$

where $[\cdot,\cdot]$ denotes the commutator bracket $\left[\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T, \mathbf{C}\right] := \underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T\mathbf{C} - \mathbf{C}\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T$. Next, consider the two expressions

$$\begin{aligned}\mathbf{A}\mathbf{V}\frac{\partial \underset{\sim}{\Sigma}^T}{\partial a_{ij}} + \mathbf{U}\frac{\partial \underset{\sim}{\Sigma}}{\partial a_{ij}}\underset{\sim}{\Sigma}^T &= \mathbf{U}\underset{\sim}{\Sigma}\frac{\partial \underset{\sim}{\Sigma}^T}{\partial a_{ij}} + \mathbf{U}\frac{\partial \underset{\sim}{\Sigma}}{\partial a_{ij}}\underset{\sim}{\Sigma}^T \\ &= \mathbf{U}\frac{\partial}{\partial a_{ij}}\left[\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T\right].\end{aligned}$$

Now consider the remaining two expressions

$$\begin{aligned}\mathbf{A}\frac{\partial \mathbf{A}^T}{\partial a_{ij}}\mathbf{U} + \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{V}\underset{\sim}{\Sigma}^T &= \mathbf{A}\frac{\partial \mathbf{A}^T}{\partial a_{ij}}\mathbf{U} + \frac{\partial \mathbf{A}}{\partial a_{ij}}\mathbf{A}^T\mathbf{U} \\ &= \left(\frac{\partial}{\partial a_{ij}}\left[\mathbf{A}\mathbf{A}^T\right]\right)\mathbf{U}.\end{aligned}$$

Using these simplifications in notation gives the system of equations in ${c_k}^{(l)}$

$$\mathbf{U}\left[\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T, \mathbf{C}\right] = \mathbf{U}\frac{\partial}{\partial a_{ij}}\left[\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T\right] - \left(\frac{\partial}{\partial a_{ij}}\left[\mathbf{A}\mathbf{A}^T\right]\right)\mathbf{U}.$$

Using the unitary condition $\mathbf{U}^T\mathbf{U} = \mathbf{I}$, where $\mathbf{I}$ is the $M \times M$ identity matrix, this equation simplifies to the final form

$$\left[\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T, \mathbf{C}\right] = \frac{\partial}{\partial a_{ij}}\left[\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T\right] - \mathbf{U}^T\left(\frac{\partial}{\partial a_{ij}}\left[\mathbf{A}\mathbf{A}^T\right]\right)\mathbf{U}. \tag{43}$$

Expanding the commutator bracket we find that

$$\left[\underset{\sim}{\Sigma}\underset{\sim}{\Sigma}^T, \mathbf{C}\right]_{kl} = \begin{cases} 0 & k = l \text{ or } k \text{ and } l > r, \\ {c_k}^{(l)}\left((\sigma_k)^2 - (\sigma_l)^2\right) & k, l \le r, \\ -{c_k}^{(l)}(\sigma_l)^2 & l \le r \text{ and } k \ge r+1, \\ {c_k}^{(l)}(\sigma_k)^2 & k \le r \text{ and } l \ge r+1. \end{cases} \tag{44}$$

Since the right side of Equation (43) is known, and since we have assumed that the singular values are distinct, we can solve for the off-diagonal coefficients.

The final task is to find the values of the diagonal coefficients. Once again, we make use of the fact that the singular vectors $\{\mathbf{u}^{(k)}\}$ form a basis for $\mathbb{R}^M$, that is, for a fixed eigenvector $\mathbf{u}^{(k)}$, the derivative is expanded as the sum

$$\frac{\partial \mathbf{u}^{(k)}}{\partial a_{ij}} = {c_1}^{(k)}\mathbf{u}^{(1)} + \cdots + {c_k}^{(k)}\mathbf{u}^{(k)} + \cdots {c_M}^{(k)}\mathbf{u}^{(M)}.$$

When we use the orthogonality of the derivative of the singular vector with the singular vector we get

$$c_1{}^{(k)}\langle \mathbf{u}^{(1)}, \mathbf{u}^{(k)}\rangle + \cdots + c_k{}^{(k)}\langle \mathbf{u}^{(k)}, \mathbf{u}^{(k)}\rangle + \cdots c_M{}^{(k)}\langle \mathbf{u}^{(M)}, \mathbf{u}^{(k)}\rangle = 0.$$

Since the individual singular vectors are orthonormal, the diagonal coefficients are all identically zero.

Using this same approach, we can find $\partial \mathbf{V}/\partial a_{ij}$. To accomplish this, write this derivative as a linear combination of the singular vectors $\mathbf{v}^{(k)}$

$$\frac{\partial \mathbf{V}}{\partial a_{ij}} = \mathbf{V}\mathbf{D},$$

where

$$\mathbf{D} := \begin{pmatrix} d_1{}^{(1)} & d_1{}^{(2)} & d_1{}^{(3)} & \cdots & d_1{}^{(N)} \\ d_2{}^{(1)} & d_2{}^{(2)} & d_2{}^{(3)} & \cdots & d_2{}^{(N)} \\ \vdots & & \vdots & & \vdots \\ d_N{}^{(1)} & d_N{}^{(2)} & d_N{}^{(3)} & \cdots & d_N{}^{(N)} \end{pmatrix},$$

and proceed as was done above.

5 Initial Value Problem

We now extend the initial value problem (IVP) (3) and (4) as the more general system of equations

$$\frac{du_1}{dt} = f_1(u_1, u_2, p_1, p_2, p_3) \qquad u_1(0) = u_1{}^{(0)} \tag{45}$$

$$\frac{du_2}{dt} = f_2(u_1, u_2, p_1, p_2, p_3) \qquad u_2(0) = u_2{}^{(0)} \tag{46}$$

where the $u_1(t)$ and $u_2(t)$ denote the time dependent forward solutions, p_1, p_2, p_3 denote some fixed or steady state parameters, $u_1{}^{(0)}$, $u_2{}^{(0)}$ are the initial conditions (IC's), and $t \in [0, b]$. To determine the sensitivity of an associated functional, or response function, of the solution, we consider a generic form that encompasses most functionals that one encounters [2, 13];

$$J[\mathbf{u}] := \int_{t=0}^{b} g(u_1, u_2, p_1, p_2, p_3)\, dt + h(u_1, u_2, p_1, p_2, p_3)\Big|_{t=b}. \tag{47}$$

Here the functions g and h are sufficiently differentiable in their arguments. We wish to determine how the functional J is affected by changes to the parameters or IC's. Specifically, we must calculate the derivatives

$$\frac{\partial J}{\partial p_1} = \int_{t=0}^{b} \left(\frac{\partial g}{\partial u_1}\frac{\partial u_1}{\partial p_1} + \frac{\partial g}{\partial u_2}\frac{\partial u_2}{\partial p_1} + \frac{\partial g}{\partial p_1} \right) dt + \left(\frac{\partial h}{\partial u_1}\frac{\partial u_1}{\partial p_1} + \frac{\partial h}{\partial u_2}\frac{\partial u_2}{\partial p_1} + \frac{\partial h}{\partial p_1} \right)\Bigg|_{t=b}$$

$$\frac{\partial J}{\partial p_2} = \int_{t=0}^{b} \left(\frac{\partial g}{\partial u_1}\frac{\partial u_1}{\partial p_2} + \frac{\partial g}{\partial u_2}\frac{\partial u_2}{\partial p_2} + \frac{\partial g}{\partial p_2} \right) dt + \left(\frac{\partial h}{\partial u_1}\frac{\partial u_1}{\partial p_2} + \frac{\partial h}{\partial u_2}\frac{\partial u_2}{\partial p_2} + \frac{\partial h}{\partial p_2} \right)\Bigg|_{t=b}$$

$$\frac{\partial J}{\partial p_3} = \int_{t=0}^{b} \left(\frac{\partial g}{\partial u_1}\frac{\partial u_1}{\partial p_3} + \frac{\partial g}{\partial u_2}\frac{\partial u_2}{\partial p_3} + \frac{\partial g}{\partial p_3} \right) dt + \left(\frac{\partial h}{\partial u_1}\frac{\partial u_1}{\partial p_3} + \frac{\partial h}{\partial u_2}\frac{\partial u_2}{\partial p_3} + \frac{\partial h}{\partial p_3} \right)\Bigg|_{t=b}$$

$$\frac{\partial J}{\partial u_1{}^{(0)}} = \int_{t=0}^{b} \left(\frac{\partial g}{\partial u_1}\frac{\partial u_1}{\partial u_1{}^{(0)}} + \frac{\partial g}{\partial u_2}\frac{\partial u_2}{\partial u_1{}^{(0)}} \right) dt + \left(\frac{\partial h}{\partial u_1}\frac{\partial u_1}{\partial u_1{}^{(0)}} + \frac{\partial h}{\partial u_2}\frac{\partial u_2}{\partial u_1{}^{(0)}} \right)\Bigg|_{t=b}$$

$$\frac{\partial J}{\partial u_2{}^{(0)}} = \int_{t=0}^{b} \left(\frac{\partial g}{\partial u_1}\frac{\partial u_1}{\partial u_2{}^{(0)}} + \frac{\partial g}{\partial u_2}\frac{\partial u_2}{\partial u_2{}^{(0)}} \right) dt + \left(\frac{\partial h}{\partial u_1}\frac{\partial u_1}{\partial u_2{}^{(0)}} + \frac{\partial h}{\partial u_2}\frac{\partial u_2}{\partial u_2{}^{(0)}} \right)\Bigg|_{t=b}.$$

5.1 Forward Sensitivity of the IVP

To evaluate the functional, all of the derivative terms $\partial u_1/\partial p_1$, $\partial u_1/\partial p_2$, etc., must be found. We start by differentiating the original IVP given in Equations (45), (46) wrt. all of the parameters and ICs. Assuming that the derivative operators d/dt and

$\partial/\partial p$ commute, the forward sensitivity equations (FSE) are given by

$$\begin{aligned}
\frac{d}{dt}\left[\frac{\partial u_1}{\partial p_1}\right] &= \frac{\partial f_1}{\partial u_1}\frac{\partial u_1}{\partial p_1} + \frac{\partial f_1}{\partial u_2}\frac{\partial u_2}{\partial p_1} + \frac{\partial f_1}{\partial p_1} \\
\frac{d}{dt}\left[\frac{\partial u_1}{\partial p_2}\right] &= \frac{\partial f_1}{\partial u_1}\frac{\partial u_1}{\partial p_2} + \frac{\partial f_1}{\partial u_2}\frac{\partial u_2}{\partial p_2} + \frac{\partial f_1}{\partial p_2} \\
\frac{d}{dt}\left[\frac{\partial u_1}{\partial p_3}\right] &= \frac{\partial f_1}{\partial u_1}\frac{\partial u_1}{\partial p_3} + \frac{\partial f_1}{\partial u_2}\frac{\partial u_2}{\partial p_3} + \frac{\partial f_1}{\partial p_3} \\
\frac{d}{dt}\left[\frac{\partial u_1}{\partial u_1{}^{(0)}}\right] &= \frac{\partial f_1}{\partial u_1}\frac{\partial u_1}{\partial u_1{}^{(0)}} + \frac{\partial f_1}{\partial u_2}\frac{\partial u_2}{\partial u_1{}^{(0)}} \\
\frac{d}{dt}\left[\frac{\partial u_1}{\partial u_2{}^{(0)}}\right] &= \frac{\partial f_1}{\partial u_1}\frac{\partial u_1}{\partial u_2{}^{(0)}} + \frac{\partial f_1}{\partial u_2}\frac{\partial u_2}{\partial u_2{}^{(0)}} \\
\frac{d}{dt}\left[\frac{\partial u_2}{\partial p_1}\right] &= \frac{\partial f_2}{\partial u_1}\frac{\partial u_1}{\partial p_1} + \frac{\partial f_2}{\partial u_2}\frac{\partial u_2}{\partial p_1} + \frac{\partial f_2}{\partial p_1} \\
\frac{d}{dt}\left[\frac{\partial u_2}{\partial p_2}\right] &= \frac{\partial f_2}{\partial u_1}\frac{\partial u_1}{\partial p_2} + \frac{\partial f_2}{\partial u_2}\frac{\partial u_2}{\partial p_2} + \frac{\partial f_2}{\partial p_2} \\
\frac{d}{dt}\left[\frac{\partial u_2}{\partial p_3}\right] &= \frac{\partial f_2}{\partial u_1}\frac{\partial u_1}{\partial p_3} + \frac{\partial f_2}{\partial u_2}\frac{\partial u_2}{\partial p_3} + \frac{\partial f_2}{\partial p_3} \\
\frac{d}{dt}\left[\frac{\partial u_2}{\partial u_1{}^{(0)}}\right] &= \frac{\partial f_2}{\partial u_1}\frac{\partial u_1}{\partial u_1{}^{(0)}} + \frac{\partial f_2}{\partial u_2}\frac{\partial u_2}{\partial u_1{}^{(0)}} \\
\frac{d}{dt}\left[\frac{\partial u_2}{\partial u_2{}^{(0)}}\right] &= \frac{\partial f_2}{\partial u_1}\frac{\partial u_1}{\partial u_2{}^{(0)}} + \frac{\partial f_2}{\partial u_2}\frac{\partial u_2}{\partial u_2{}^{(0)}}.
\end{aligned}$$

In full FSA, the parameter FSE's entails a total of six separate numerical solutions perturbing each of the parameters, while the set of IC's FSE's requires a total of four additional numerical runs perturbing each of the ICs. A significant drawback of FSA is the proliferation of equations that occurs in the SA. In this example, we had to introduce ten additional equations, six for the parameters and four for the IC's. When working with large systems of IVPs, performing a FSA can be computationally prohibitive. Suppose that the original system of IVPs consists of j equations and, hence, j initial conditions. If there are k parameters, then the total number of IVPs that must be solved is $j(j + k + 1)$. For example, in constructing an age structured epidemiological model, it would not be unreasonable to have 10 equations with 20 parameters. In this simple case, to do a full FSA we would need to solve a total of 310 IVPs. A 31-fold increase in the number of equations needed to do a sensitivity analysis is a significant computational burden.

Sometimes this computational burden can be reduced if you are only interested in obtaining the numerical estimation of some of the FSEs. Suppose that you were

interested in only $\partial u_2/\partial p_3$, then you could note that only other IVP that is involved with this equation is the equation for $(d/dt)[\partial u_1/\partial p_3]$ and these two equations together do not involve any of the other FSEs. Therefore, only these two FSE's along with the original forward problem need to be solved.

Before discussing the adjoint approach, we summarize the procedure for finding the FSE of the general first order IVP

$$\frac{\mathrm{d}\mathbf{u}}{\mathrm{d}t} = \mathbf{F}[\mathbf{u}(t;\mathbf{p})], \qquad \mathbf{u}(0) = \mathbf{u}_0, \tag{48}$$

where $\mathbf{u}$ is an $n \times 1$ forward solution vector and $\mathbf{p}$ is an $(k + n) \times 1$ vector which represents any of the k parameters or n initial conditions associated with the problem.

Differentiating the forward problem wrt. $\mathbf{p}$ produces the FSE

$$\frac{\mathrm{d}}{\mathrm{d}t}\left[\mathbf{D}_\mathbf{p}[\mathbf{u}]\right] = \mathbf{D}_\mathbf{u}[\mathbf{F}] \cdot \mathbf{D}_\mathbf{p}[\mathbf{u}] + \mathbf{D}_\mathbf{p}[\mathbf{F}], \tag{49}$$

where $\mathbf{D}_\mathbf{p}[\mathbf{u}]$ is the $n \times (k + n)$ Jacobian of $\mathbf{u}$, wrt. the parameters $\mathbf{p}$ and IC's $\mathbf{u}^{(0)}$, $\mathbf{D}_\mathbf{u}[\mathbf{F}]$ is the $n \times n$ Jacobian of $\mathbf{F}$, wrt. the forward solution $\mathbf{u}$, and $\mathbf{D}_\mathbf{p}[\mathbf{F}]$ is the $n \times (k+n)$ Jacobian of $\mathbf{F}$, with respect to the parameters $\mathbf{p}$ and IC's $\mathbf{u}^{(0)}$. To calculate the derivatives which define $\mathbf{D}_\mathbf{p}[\mathbf{u}]$, both the forward problem-IVP and the FSEs given in Equations (48) and (49) respectively must be solved simultaneously. The IC's for the FSE is determined by the choice of parameter of interest. Notice that in solving the FSE, the derivatives are obtained, in which case the Jacobian $\mathbf{D}_\mathbf{p}[\mathbf{u}]$ is found.

If the sensitivity of an associated function(al) J is needed, then we must calculate the derivatives of J with respect to each component of the vector $\mathbf{p}$;

$$\frac{\mathrm{d}J}{\mathrm{d}\mathbf{p}} = \int_{t=0}^{b} \left(\mathbf{D}_\mathbf{p}{}^T[\mathbf{u}]\nabla_\mathrm{u} g + \nabla_\mathrm{p} g\right)\, dt + \left(\mathbf{D}_\mathbf{p}{}^T[\mathbf{u}]\nabla_\mathrm{u} h + \nabla_\mathrm{p} h\right)\Big|_{t=b}. \tag{50}$$

As was noted above, the term $\mathbf{D}_\mathbf{p}{}^T[\mathbf{u}]$ obtained from the FSE's is now used to find the desired derivative $\partial J/\partial \mathbf{p}$. As has been done in previous examples, we introduce an associated adjoint problem to circumvent calculating $\mathbf{D}_\mathbf{p}{}^T[\mathbf{u}]$. Specifically, by cleverly choosing the adjoint problem and adjoint boundary conditions, eventually we will eliminate/replace the expressions $\mathbf{D}_\mathbf{p}{}^T[\mathbf{u}]\nabla_\mathrm{u} g$ and $\mathbf{D}_\mathbf{p}{}^T[\mathbf{u}]\nabla_\mathrm{u} h|_{t=b}$.

5.2 Adjoint Sensitivity Analysis of the IVP

As was noted in previous examples, the next step in our analysis is to construct the associated adjoint sensitivity equations (ASE). The key was to cleverly formulate the ASE so as to eliminate the direct evaluation of $\mathbf{D}_\mathbf{p}[\mathbf{u}]$.

As in previous cases, the adjoint can be constructed only if an appropriate inner product space exists for the forward problem. In this case, the natural inner product is

$$\int_{t=0}^{b} \mathbf{v}^T \left(\frac{\mathrm{d}}{\mathrm{d}t} \left[\mathbf{D_p}[\mathbf{u}] \right] - \mathbf{D_u}[\mathbf{F}] \cdot \mathbf{D_p}[\mathbf{u}] - \mathbf{D_p}[\mathbf{F}] \right) dt = 0, \tag{51}$$

where $\mathbf{v}$ is the associated adjoint variable. Expanding the $\mathbf{v}^T$ term and using integration by parts on the first integrand gives

$$\mathbf{v}^T \mathbf{D_p}[\mathbf{u}] \Big|_{t=0}^{b} + \int_{t=0}^{b} \left(-\frac{\mathrm{d}\mathbf{v}^T}{\mathrm{d}t} - \mathbf{v}^T \mathbf{D_u}[\mathbf{F}] \right) \mathbf{D_p}[\mathbf{u}]\, dt - \int_{t=0}^{b} \mathbf{v}^T \mathbf{D_p}[\mathbf{F}]\, dt = 0. \tag{52}$$

If we compare the terms in the first integrand of this equation with the first expression in the integrand of Equation (50) notice that two expressions are similar in form. This can be seen by using the transpose operation, namely

$$(\mathbf{D_p}^T[\mathbf{u}] \nabla_{\mathrm{u}} g)^T = (\nabla_{\mathrm{u}} g)^T \mathbf{D_p}[\mathbf{u}], \tag{53}$$

in which case we force the adjoint condition

$$-\frac{\mathrm{d}\mathbf{v}^T}{\mathrm{d}t} - \mathbf{v}^T \mathbf{D_u}[\mathbf{F}] = (\nabla_{\mathrm{u}} g)^T \tag{54}$$

Substituting and rearranging gives

$$\int_{t=0}^{b} (\nabla_{\mathrm{u}} g)^T \ \mathbf{D_p}[\mathbf{u}]\, dt = \int_{t=0}^{b} \mathbf{v}^T \mathbf{D_p}[\mathbf{F}]\, dt - \mathbf{v}^T \mathbf{D_p}[\mathbf{u}] \Big|_{t=b}. \tag{55}$$

Take the transpose and substitute into the right hand side of dJ/dp

$$\frac{\mathrm{d}J}{\mathrm{d}\mathbf{p}} = \int_{t=0}^{b} (\mathbf{D_p}^T[\mathbf{F}]\mathbf{v} + \nabla_{\mathrm{p}} g)\, dt - \mathbf{D_p}^T[\mathbf{u}] \Big|_{t=0}^{b} + (\mathbf{D_p}^T[\mathbf{u}] \nabla_{\mathrm{u}} h + \nabla_{\mathrm{p}} h) \Big|_{t=b}. \tag{56}$$

Notice that in this formulation, the definite integral does not contain the expression $\mathbf{D_p}^T[\mathbf{u}]$, only the boundary conditions contain this expression. Since $\mathbf{D_p}^T[\mathbf{u}]|_{t=0}$ is easily calculated while the expression $\mathbf{D_p}^T[\mathbf{u}]|_{t=b}$ can only be calculated by integrating the FSE's for $t \in [0, b]$, we can eliminate the upper BC by forcing

$$v(b) := \nabla_{\mathrm{u}} h \Big|_{t=b}, \tag{57}$$

which reduces the expression for the derivative of J to be

$$\frac{\mathrm{d}J}{\mathrm{d}\mathbf{p}} = \int_{t=0}^{b} (\mathbf{D_p}^T[\mathbf{F}]\mathbf{v} + \nabla_{\mathrm{p}} g)\, dt + \mathbf{D_p}^T[\mathbf{u}]\mathbf{v}\Big|_{t=0} + \nabla_{\mathrm{p}} h\Big|_{t=b}. \tag{58}$$

Once again, by creating an associated adjoint problem, with appropriately chosen BC's, we are able to circumvent the problem of having to calculate $\mathbf{D_p}[\mathbf{u}]$.

6 Principal Component Analysis of the IVP

6.1 Multiparameter Variation

In the previous section we constructed the FSEs for the IVP and obtained local time dependent sensitivities for fixed parameter values. It was quite evident that as the number of IVPs and parameters increase, the calculation of the FSEs becomes burdensome. In this situation, the adjoint methodology becomes a more practical alternative. With these limitations in mind, we now consider the case where the FSEs are not too cumbersome to solve. With this caveat, suppose that the parameter vector $\mathbf{p} = (p_1\ p_2\ \ldots\ p_K)^T$ has an uncertainty, that is, the parameters are not specified as precise values, but rather are given as some distribution, with expected value vector $\mathbb{E}[\mathbf{p}] = \mu_{\mathbf{p}}$. The distinction between this analysis and previous results is that here we wish to quantify the effects of uncertainty for multiparameter variations. In other words, we wish to estimate the variation of the output, due to the effective strength of coupling between parameters.

For "small" perturbations $\delta\mathbf{p} := \mathbf{p} - \mu_{\mathbf{p}}$ to the parameter vector, the variation of the output, to first order terms, is given by

$$\delta\mathbf{u} := \mathbf{u}(t; \mu_{\mathbf{p}} + \delta\mathbf{p}) - \mathbf{u}(t; \mu_{\mathbf{p}}) \approx \mathbf{D_p}[\mathbf{u}]\delta\mathbf{p},$$

where as above, $\mathbf{D_p}[\mathbf{u}]$ denotes the Jacobian of $\mathbf{u}$, wrt. the parameters $\mathbf{p}$. Now take the outer product $\delta\mathbf{u} \otimes \delta\mathbf{u} = \delta\mathbf{u} \cdot \delta\mathbf{u}^T$, to obtain an approximation of the variation matrix of the output

$$\delta\mathbf{u} \cdot \delta\mathbf{u}^T \approx \mathbf{D_p}[\mathbf{u}]\ \delta\mathbf{p} \cdot \delta\mathbf{p}^T\ \mathbf{D_p}[\mathbf{u}]^T. \tag{59}$$

Without giving all the details (see pp.120–126 [5], especially equation III.F.16 page 124), it can be shown that the temporal output covariance matrix, denoted as $\mathbf{C_u}$, can be written as

$$\mathbf{C_u} = \mathbf{D_p}[\mathbf{u}]\ \mathbb{E}\left[\delta\mathbf{p} \cdot \delta\mathbf{p}^T\right]\ \mathbf{D_p}[\mathbf{u}]^T. \tag{60}$$

This time dependent matrix provides an approximation to the evolution of how the coupling in the parameter variation affects the output.

Since covariance matrices are symmetric, we are guaranteed (see [15]) to have a decomposition of $\mathbf{C_u}$ given by

$$\mathbf{C_u} = \mathbf{Q} \underset{\sim}{\Lambda} \mathbf{Q}^T = \sum_{i=1}^{K} \lambda_i \mathbf{q}_i(t) \cdot \mathbf{q}_i{}^T(t), \tag{61}$$

where $\mathbf{Q}$ is an orthonormal matrix whose columns consist of the eigenvectors $\mathbf{q}_i(t)$, for $i = 1, \ldots, K$, of $\mathbf{C_u}$, and $\underset{\sim}{\Lambda}$ is a diagonal matrix whose entries are the associated eigenvalues, λ_i, written in decreasing order. Using this result we can examine the effect of multiparameter variation in the principal component space. To accomplish this, consider the transformation from solution space to principal component space given by

$$\mathbf{v} := \mathbf{Q}^T \left(\mathbf{u}(t; \mu_\mathbf{p} + \delta\mathbf{p}) - \mathbf{u}(t; \mu_\mathbf{p}) \right) \approx \mathbf{Q}^T \mathbf{D_p}[\mathbf{u}] \delta\mathbf{p}.$$

Taking the outer product $\mathbf{v} \otimes \mathbf{v}$ allows us to define the covariance matrix $\mathbf{C}_{\text{PCS}}$ in pricipal component space as

$$\begin{aligned} \mathbf{C}_{\text{PCS}} &= \mathbf{Q}^T \ \mathbf{D_p}[\mathbf{u}] \ \mathbb{E}\left[\delta\mathbf{p} \cdot \delta\mathbf{p}^T\right] \ \mathbf{D_p}[\mathbf{u}]^T \mathbf{Q} \\ &= \mathbf{Q}^T \mathbf{C_u} \mathbf{Q} \\ &= \mathbf{Q}^T \ \mathbf{Q} \underset{\sim}{\Lambda} \mathbf{Q}^T \mathbf{Q} \\ &= \underset{\sim}{\Lambda}. \end{aligned}$$

Notice that the covariance matrix $\mathbf{C}_{\text{PCS}}$ is a diagonal matrix, which means that the transformed vectors in principal component space are independent. Furthermore, since the diagonal contains the eigenvalues, in decreasing order, the transformed vectors are projected along the principal component axes formed by the eigenvectors and in decreasing variance. This means that the greatest variation of $\mathbf{v}$ occurs along the first eigenvector $\mathbf{q}_1(t)$ with variance λ_1, the second largest variation occurs along $\mathbf{q}_2(t)$ with variance λ_2, etc.

7 Algorithmic Differentiation

When the problem of interest is to "find the derivative," we must be careful to distinguish which of the following two objectives we trying to accomplish:

1. explicitly finding a symbolic expression for the derivative, or
2. numerically estimating the derivative by a discrete approximation, such as finite difference or a finite element method.

The main focus of previous sections was to explicitly find the ubiquitous derivative in various settings. We discussed how to find the derivative of an output variable wrt. a particular parameter, or input variable. In this section, we provide a cursory introduction to the methodology of algorithmic differentiation (AD), that is, how a computer differentiates a algorithm. Since the researcher in epidemiology will eventually want to numerically calculate derivatives, without having to write computer code to accomplish this, standard packages such as ADIFOR, ADOL-C, ADOL-F, DAFOR, TAMC, etc., should be used [25]. This section provides the basic background needed in order to understand how AD works.

7.1 Sensitivity of the Reproductive Number R_0

We introduce the AD methodology in a familiar epidemiological setting by considering the SEIR model

$$\begin{aligned}
\frac{dS}{dt} &= bN - \mu S - \beta S \frac{I}{N} \\
\frac{dE}{dt} &= \beta S \frac{I}{N} - (\mu + k) E \\
\frac{dI}{dt} &= kE - (r + \mu) I \\
\frac{dR}{dt} &= rI - \mu R,
\end{aligned}$$

where S, E, I, and R denote the susceptible, exposed, infectious, and recovered populations respectively, and $N = S + E + I + R$ is the total population. The parameter β quantifies the efficacy of the infection in the susceptible population, k is the per capita rate at which the exposed population becomes infectious, μ is the per capita death rate, r is the per capita recovery rate, and b is the intrinsic birth/migration rate.

A commonly used measure of the intensity of the infection is the basic reproductive number R_0 of the average number of susceptible individuals who have been infected by a particular infectious individual, over the lifetime of that infected individual. If $R_0 < 1$, then on average, each infectious individual infects less than one other individual, in which case we expect the infection to eventually subside. If $R_0 > 1$, then the infection is expected to spread throughout the susceptible population. This threshold condition provides a mathematical criteria for determining whether the infection will spread or subside. Additionally, since R_0 depends on the parameters of the model, SA provides a way to measure which parameters have the most effect on the spread or decrease in the infection.

A particular problem in obtaining R_0 is that there are numerous ways, which have specific strengths/weaknesses, of deriving R_0. Three of the most used approaches to derive R_0 are:

- Survival function method: This method is appropriate when explicit expressions are available for the survival probability, (probability that a newly infected individual remains infectious for time t) and the infectivity as a function of time.
- Next generation method: This method is appropriate when the population can naturally be divided into discrete and disjoint classes, such as age, social status (e.g., prostitute, day care worker, drug addict, etc..), demographic region, etc.
- Surrogate methods: The key concepts are the stability of the disease free equilibrium point, locating a transcritical bifurcation of the endemic equilibrium, etc.

The R_0 for the above SEIR model is given by

$$R_0 := \frac{k\beta}{(r+\mu)(k+\mu)}. \tag{62}$$

Because the parameter values depend on the particular strain of infection, R_0 will also depend on the specific infection. For example, consider the potentially life threatening flu, which we broadly categorize in two forms: (1) seasonal flu, with $R_0 \approx 1.5$, and (2) pandemic flu[2] with $R_0 \in [2, 3]$. For *illustrative purposes only*, the seasonal flu will be modeled using the parameter values, in dimensional units of days^{-1}, of $\beta = 0.375$, $k = 0.5$, $\mu = 3.7 \times 10^{-5}$), and $r = 0.25$, in which case $R_0 \approx 1.499$. Since the reproductive number is greater than 1, the infection is expected to spread. SA may now be used to determine how sensitive the spread is to each of the defining parameters.

For example suppose, through some intervention strategy, we are able to slightly alter the value of the parameter r, then the SI

$$SI_r = -\left(\frac{r}{r+\mu}\right) = -0.999852 < 0,$$

tells us that if we increase r by approximately 1%, then R_0 decreases by approximately 1%, and vice versa. This is easily verified by increasing $r : 0.25 \to 0.2525$, which decreases $R_0 : 1.49967 \to 1.48482$ and results in a -0.989954% decrease in R_0, as estimated from the normalized SI.

A significant advantage of having this type of local analysis available is that now the powerful tool of cost-benefit analysis is available. If the sensitivity of hypothetical intervention strategy **A** is $SI_1 = 0.75$ with associated cost of $\$1 \times 10^4$, while

[2] Recall the devastating 1918–1919 influenza pandemic: "An estimated one third of the world's population (or $\approx$ 500 million persons) were infected and had clinically apparent illnesses during the 1918–1919 influenza pandemic. The disease was exceptionally severe. Case-fatality rates were $> 2.5\%$, compared to $< 0.1\%$ in other influenza pandemics. Total deaths were estimated at $\approx$ 50 million and were arguably as high as 100 million." [14]

the sensitivity of intervention strategy **B** is $SI_2 = -0.25$ with associated cost of $\$4 \times 10^3$, then the cost-benefit ratios are

$$CB_1 = \frac{\$1 \times 10^4}{|0.75|} = \frac{\$13.3 \times 10^3}{\text{unit}}, \quad \text{and} \quad CB_2 = \frac{\$4 \times 10^3}{|-0.25|} = \frac{\$16 \times 10^4}{\text{unit}}.$$

All other things being equal, since the first cost-benefit ratio is the smaller, this suggests that intervention strategy **A** should be implemented. It should be noted that the signs of the SIs and input and output variables be examined carefully, as was noted in the beginning section discussing the definition of the SI.

7.2 Forward Sensitivity/Mode

We now describe the main idea behind AD, in the *forward mode*, without discussing any of the coding quality, rounding, memory allocation, computational overhead, etc., topics that are inherent to the actual implementation and execution of AD [25]. The basic idea in AD is quite simple, however the actual implementation is rather sophisticated. Essentially, AD is an automatic implementation of the standard chain rule from calculus. For example, consider the formal differential operations

$$\begin{aligned} d\left[\frac{u}{v^2}\right] &= \frac{v^2\,du - u\,d\left[v^2\right]}{(v^2)^2} \\ &= \frac{v^2\,du - u\,(2v\,dv)}{v^4}. \end{aligned}$$

The basic algebraic and differential operations performed were applications of the

- derivative of a quotient,
- derivative of a function to a power, and
- algebraic simplification rule of a base to an exponent, to another exponent.

In the jargon of AD, the standard rules of calculus would be written as the "tangent operations," using the elemental differentials in Fig. 6, and pseudo code for

$\square = c$ $d\square = 0$
$\square = \triangle \pm \heartsuit$ $d\square = d\triangle \pm d\heartsuit$
$\square = \triangle * \heartsuit$ $d\square = d\triangle * \heartsuit + \triangle * d\heartsuit$
$\square = \triangle / \heartsuit$ $d\square = (\heartsuit * d\triangle - \triangle * d\heartsuit)/(\heartsuit^2)$
etc.

Fig. 6 Templates used in AD for the standard rules of calculus, where the symbols $\square$, $\triangle$, and $\heartsuit$ denote "elemental functions", and the symbols $d\triangle$ and $d\heartsuit$ denote the "elemental differentials"

calculating the SI of R_0 wrt. r, is first defined without any attempt at efficient coding.

The first step is the initialization of the parameters.

$$
\begin{aligned}
&p\_1 = 0.375; && // \quad p_1 = \beta \\
&p\_2 = 0.5; && // \quad p_2 = k \\
&p\_3 = 3.7 * (10\hat{}(-5)); && // \quad p_3 = \mu \\
&p\_4 = 0.25; && // \quad p_4 = r
\end{aligned}
$$

Our intention is to calculate the normalized SI wrt. the parameter r, while the other parameters β, k, and μ are constant. Therefore, we initialize the derivatives as

$$
\begin{aligned}
&dp\_1 = 0.0; && // \quad \partial\beta/\partial r = 0 \\
&dp\_2 = 0.0; && // \quad \partial k/\partial r = 0 \\
&dp\_3 = 0.0; && // \quad \partial\mu/\partial r = 0 \\
&dp\_4 = 1.0; && // \quad \partial r/\partial r = 1
\end{aligned}
$$

In the jargon of AD, $p_1, \ldots, p_4, dp_1, \ldots, dp_4$ are referred to as the input variables.

Next, we perform the forward evaluation of the intermediate variables $u_1 = k\beta$, $u_2 = r + \mu$, $u_3 = k + \mu$, and $u_4 = (r + \mu)(k + \mu)$, along with the associated derivatives.

$$
\begin{aligned}
&u\_1 = p\_2 * p\_1 = 0.1875; && // \quad u_1 = k\beta \\
&du\_1 = p\_2 * dp\_1 + dp\_2 * p\_1 = 0.0; && // \quad \frac{\partial u_1}{\partial r} = k\frac{\partial \beta}{\partial r} + \frac{\partial k}{\partial r}\beta = 0 \\
&u\_2 = p\_4 + p\_3 = 0.250038; && // \quad u_2 = r + \mu = 0.250038 \\
&du\_2 = dp\_4 + dp\_3 = 1.0; && // \quad \frac{\partial u_2}{\partial r} = \frac{\partial r}{\partial r} + \frac{\partial \mu}{\partial r} = 1.0 \\
&u\_3 = p\_2 + p\_3 = 0.500038; && // \quad u_3 = k + \mu = 0.500038 \\
&du\_3 = dp\_2 + dp\_3 = 0.0; && // \quad \frac{\partial u_3}{\partial r} = \frac{\partial k}{\partial r} + \frac{\partial \mu}{\partial r} = 0.0. \\
&u\_4 = u\_2 * u\_3 = 0.125028; && // \quad \begin{aligned} u_4 &= (r + \mu)(k + \mu) \\ &= 0.125028 \end{aligned} \\
&du\_4 = u\_2 * du\_3 + du\_2 * u\_3 = 0.500038; && // \quad \begin{aligned} \frac{\partial u_4}{\partial r} &= \frac{\partial}{\partial r}[(r + \mu)(k + \mu)] \\ &= 0.500038 \end{aligned}
\end{aligned}
$$

Now form the reproductive number

$$R_0 = u_5 = \frac{u_1}{u_4} = \frac{u_1}{u_2 u_3} = \frac{\overbrace{k\beta}^{u_1}}{\underbrace{(r+\mu)}_{u_2}\underbrace{(k+\mu)}_{u_3}} \tag{63}$$

and the derivative $\partial R_0/\partial r$.

$$u\_5 = u\_1/u\_4 = 1.49967; \qquad // \quad \begin{aligned} u_5 &= \frac{k\beta}{(r+\mu)(k+\mu)} \\ &= 1.49967 \end{aligned}$$

$$du\_5 = (u\_4 * du\_1 - u\_1 * du\_4)/$$

$$(u\_4)^2 = -5.99778; \qquad // \quad \begin{aligned} \frac{\partial u_5}{\partial r} &= \frac{\partial}{\partial r}\left[\frac{k\beta}{(r+\mu)(k+\mu)}\right] \\ &= -5.99778 \end{aligned}$$

Finally, the SI is calculated, as the output variable u_6

$$u\_6 = (p\_4/u\_5) * du\_5 = -0.999852?; \qquad // \quad \begin{aligned} u_6 &= \frac{r}{R_0}\frac{\partial R_0}{\partial r} \\ &= -0.999852 \end{aligned}$$

as was found by direct calculation.

The above pseudo code for calculating, in the forward mode, the SI $(r/R_0)\partial R_0/\partial r$ provides a glimpse into how AD is done. The execution of AD is that as one intermediate calculation is completed, that result, along with other intermediate results, become inputs for subsequent calculations. Furthermore, each forward evaluation is also differentiated as well. Evaluation of these functions can be thought of as the progression through a directed tree[3], with vertices $p_1, \ldots, p_4, u_1, \ldots, u_6$, and SI_{R_0} as shown in Fig. 7. The input/independent variables, denoted as $p_1, \ldots, p_4$ are referred to as the roots of the graph, and the leaves of the graph are the dependent variables $u_1, \ldots, u_6$, and SI_{R_0}. The standard convention is to place the roots to the left, and the leaves to the right in the graph.

As another unrelated however instructive example, consider the sequence of computations

$$u_1 := f_1[p_1, p_3]; \quad u_2 := f_2[p_2, u_1]; \quad u_3 := f_3[p_1, p_2, p_4, u_2];$$
$$u_4 := f_4[p_2, u_2, u_3]; \quad u := u_4;$$

[3] We are assuming that this particular algorithm does not have any loops, in which case the graph has no cycles, which means the graph will be a tree. In the more general case, this restriction is not necessary as sophisticated AD packages can handle these complications.

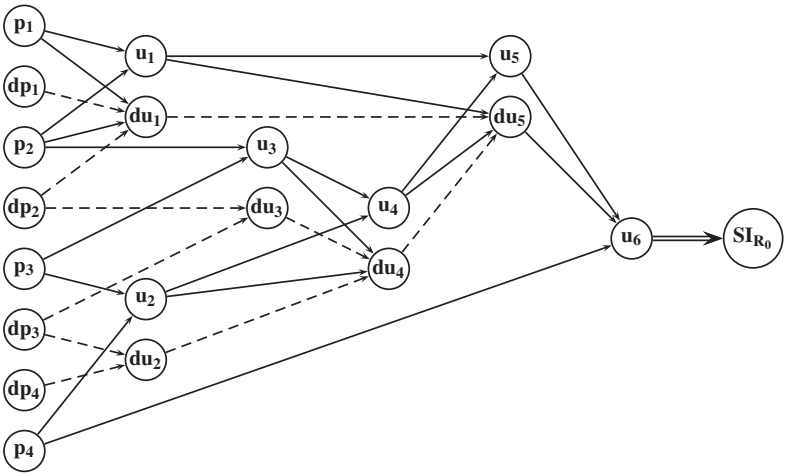

Fig. 7 Directed computational graph for R_0. *Solid arrows* denote forward evaluations and *dashed arrows* denote forward derivative evaluations. The parameters $p_1, \ldots, p_4$ and the derivative parameters $dp_1, \ldots, dp_4$ are first initialized. Next the intermediate forward variables $u_1, \ldots, u_6$ and the intermediate forward derivative variables $du_1, \ldots, du_6$ are calculated. The final step is the output variable SI_{R_0}

where $p_1, \ldots, p_4$ are the input variables, $u_1, \ldots, u_4$, are the intermediate outputs/variables, and u: final output/variable, with the associated computational graph as shown in Fig. 8

Suppose that we wish to calculate du/dp_3. In the forward mode, we start at the specified parameter p_3 and successively take derivatives of every intermediate variable by following the directed edges. Since there are two distinct directed paths from p_3 to u, namely $p_3 \to u_1 \to u_2 \to u_4 \to u$ and $p_3 \to u_1 \to u_2 \to u_3 \to u_4 \to u$, we expect that the final expression for du/dp_3 has two terms

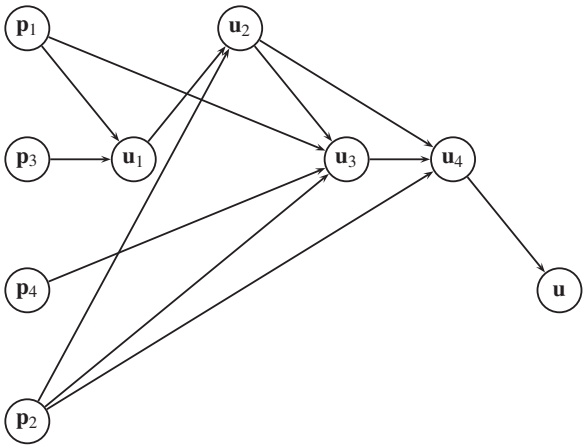

Fig. 8 Directed graph of an algorithm with input parameters $p_1, \ldots, p_4$, intermediate outputs/variables $u_1, \ldots, u_4$, and final output/variable u

reflecting this observation. If we had wanted to obtain du/dp_4, the progression would be $p_4 \to u_3 \to u_4 \to u$ and the associated derivative would contain only one expression.

Assuming that the input parameters are independent of each other, then to find du/dp_3 the following forward calculations, taken in order, are performed:

$$\frac{du_1}{dp_3} = \frac{\partial u_1}{\partial p_3}$$

$$\frac{du_2}{dp_3} = \frac{\partial u_2}{\partial u_1}\frac{du_1}{dp_3}$$

$$\frac{du_3}{dp_3} = \frac{\partial u_3}{\partial u_2}\frac{du_2}{dp_3}$$

$$\frac{du_4}{dp_3} = \frac{\partial u_4}{\partial u_2}\frac{du_2}{dp_3} + \frac{\partial u_4}{\partial u_3}\frac{du_3}{dp_3}$$

$$\frac{du}{dp_3} = \frac{\partial u}{\partial u_4}\frac{du_4}{dp_3}, \qquad \text{where} \quad \frac{\partial u}{\partial u_4} = 1$$

The actual progression needed to calculate the final output derivative is in the forward direction and the explicit output derivative is given by

$$\frac{du}{dp_3} = \underbrace{\frac{\partial u}{\partial u_4}\frac{\partial u_4}{\partial u_2}\frac{\partial u_2}{\partial u_1}\frac{\partial u_1}{\partial p_3}}_{p_3 \to u_1 \to u_2 \to u_4 \to u} + \underbrace{\frac{\partial u}{\partial u_4}\frac{\partial u_4}{\partial u_3}\frac{\partial u_3}{\partial u_2}\frac{\partial u_2}{\partial u_1}\frac{\partial u_1}{\partial p_3}}_{p_3 \to u_1 \to u_2 \to u_3 \to u_4 \to u}. \tag{64}$$

Using these examples as a template, suppose that we have K input parameters $p \in \{p_1, \ldots, p_K\}$ and N intermediate variables $u_1, \ldots, u_N$, defined as the differentiable functions $u_1 := f_1[p_1, \ldots, p_K]$, $u_i := f_i\left[p_1, \ldots, p_K, u_1, \ldots u_{i-1}\right]$, for $i = 2, \ldots N$, and the output variable only depends on u_N, i.e., $u = u_N$. The derivatives du_i/dp are given by

$$\frac{du_1}{dp} = \frac{\partial u_1}{\partial p} \tag{65}$$

$$\frac{du_i}{dp} = \sum_{j=1}^{i-1} \frac{\partial u_i}{\partial u_j}\frac{du_j}{dp} + \frac{\partial u_i}{\partial p} \tag{66}$$

$$\frac{du}{dp} = \frac{du_N}{dp} \tag{67}$$

for $i = 2, \ldots, N$.

7.3 Adjoint/Reverse Mode

In the forward mode, a particular parameter/input variable of interest was first chosen, then moving forward on the directed tree, derivatives of successive intermediate variables were taken. In the adjoint or reverse mode,[4] a final output variable is chosen and this output is differentiated wrt. each of the intermediate variables. The actual order of calculation however is reversed.

For the specific example given in Fig. 8 the differentiation proceeds as follows. The output variable u is directly affected by the intermediate variable u_4, in which case

$$\frac{du}{du_4} = \frac{\partial u_4}{\partial u_4} = 1.$$

Now u is affected by u_3 indirectly through u_4, in which case the chain rule gives

$$\frac{\partial u}{\partial u_3} = \frac{\partial u}{\partial u_4}\frac{\partial u_4}{\partial u_3} = \frac{\partial u_4}{\partial u_3}.$$

Similarly, since u_2 affects u indirectly through u_3 and u_4, then

$$\frac{\partial u}{\partial u_2} = \frac{\partial u}{\partial u_3}\frac{\partial u_3}{\partial u_2} + \frac{\partial u}{\partial u_4}\frac{\partial u_4}{\partial u_2}.$$

Lastly, u_1 affects u through u_2 and p_3 affects u through u_1, then

$$\frac{\partial u}{\partial u_1} = \frac{\partial u}{\partial u_2}\frac{\partial u_2}{\partial u_1} \qquad \text{and} \qquad \frac{\mathrm{d}u}{\mathrm{d}p} = \frac{\partial u}{\partial u_1}\frac{\partial u_1}{\partial p_3}.$$

Notice that the order of evaluation is reversed, namely, the path now taken is $\partial u/\partial u_3 \to \cdots$, and the result du/dp_3, which is obtained by the composition of the derivatives, is the same as the result given in Equation (64).

For the reproduction number example given in Fig. 7, we will only calculate $\partial R_0/\partial r = \partial u_5/\partial p_4$. To follow standard conventions in AD, define the output variable $u := u_5$, in which case we wish to calculate $\partial u/\partial p_4$.

Examining Fig. 7, ignoring the paths containing du vertices, there is only one path from p_4 to u_5, namely $p_4 \to u_2 \to u_4 \to u_5$, and since p_4 does not affect u_1, pseudo code for the reverse/adjoint mode is given by

---

[4] The reader is cautioned about the usage of the terminology "backward mode." The standard methods in numerical analysis of the BDF (Backward Differentiation Formulas), which are used in the numerical solution of stiff IVP's, are not what is being discussed in the adjoint/reverse mode of AD. Hence to avoid any confusion, we will refer to the differentiation of the output variable, wrt. each of the intermediate variables as the adjoint or reverse mode.

$$
\begin{aligned}
du\backslash du\_5 &= 1.0; && // \quad \frac{\partial u}{\partial u_5} = \frac{\partial u_5}{\partial u_5} \\
du\backslash du\_4 &= du\backslash du\_5 * du\_5\backslash du\_4 = -11.9947; && // \quad \frac{\partial u}{\partial u_4} = \frac{\partial u}{\partial u_5}\frac{\partial u_5}{\partial u_4} \\
du\backslash du\_3 &= du\backslash du\_4 * du\_4\backslash du\_3 = -2.9991; && // \quad \frac{\partial u}{\partial u_3} = \frac{\partial u}{\partial u_4}\frac{\partial u_4}{\partial u_3} \\
du\backslash du\_2 &= du\backslash du\_4 * du\_4\backslash du\_2 = -5.9998; && // \quad \frac{\partial u}{\partial u_2} = \frac{\partial u}{\partial u_4}\frac{\partial u_4}{\partial u_2} \\
du\backslash du\_1 &= du\backslash du\_5 * du\_5\backslash du\_1 = 7.9982; && // \quad \frac{\partial u}{\partial u_1} = \frac{\partial u}{\partial u_5}\frac{\partial u_5}{\partial u_1} \\
du\backslash dr &= du\backslash du\_2 * du\_2\backslash dr = -5.9979; && // \quad \frac{\partial u}{\partial p_4} = \frac{\partial u}{\partial u_2}\frac{\partial u_2}{\partial p_4}
\end{aligned}
$$

in which case $SI_{R_0} = (r/R_0)\partial R_0/\partial r = (0.25/1.49967)(-5.9979) = -0.99987$ as agrees with the previous results.

For the general problem, in the actual order they are evaluated, the ASE are given by

$$
\begin{aligned}
\frac{\partial u}{\partial u_N} &= \frac{\partial u_N}{\partial u_N} = 1 \\
\frac{\partial u}{\partial u_{N-1}} &= \frac{\partial u}{\partial u_N}\frac{\partial u_N}{\partial u_{N-1}} \\
\frac{\partial u}{\partial u_{N-2}} &= \frac{\partial u}{\partial u_{N-1}}\frac{\partial u_{N-1}}{\partial u_{N-2}} + \frac{\partial u}{\partial u_N}\frac{\partial u_N}{\partial u_{N-2}} \\
\frac{\partial u}{\partial u_{N-3}} &= \frac{\partial u}{\partial u_{N-2}}\frac{\partial u_{N-2}}{\partial u_{N-3}} + \frac{\partial u}{\partial u_{N-1}}\frac{\partial u_{N-1}}{\partial u_{N-3}} + \frac{\partial u}{\partial u_N}\frac{\partial u_N}{\partial u_{N-3}} \\
&\vdots \\
\frac{\partial u}{\partial u_1} &= \frac{\partial u}{\partial u_2}\frac{\partial u_2}{\partial u_1} + \frac{\partial u}{\partial u_3}\frac{\partial u_3}{\partial u_1} + \cdots + \frac{\partial u}{\partial u_N}\frac{\partial u_N}{\partial u_1}
\end{aligned}
\tag{68}
$$

and finally

$$
\frac{\mathrm{d}u}{\mathrm{d}p} = \sum_{i=1}^{N} \frac{\partial u}{\partial u_i}\frac{\partial u_i}{\partial p}. \tag{69}
$$

The astute reader is probably wondering why the insistence on using the phrase "adjoint mode," rather than the more transparent "reverse mode," since it is quite clear that the derivative terms are being evaluated in reverse order, as compared to the forward mode. To justify this terminology, reverse the order of the above ASE,

given in (68). Without giving all the details, this system can be concisely written in matrix form involving the transpose of the Jacobian[5] $\mathbf{D}[\mathbf{u}]$

$$\mathbf{D}[\mathbf{u}] = \begin{pmatrix} 1 & 0 & \cdots & & 0 \\ \dfrac{\partial u_2}{\partial u_1} & 1 & 0 & \cdots & 0 \\ \dfrac{\partial u_3}{\partial u_1} & \dfrac{\partial u_3}{\partial u_2} & 1 & 0 \quad \cdots & 0 \\ \vdots & \vdots & & \ddots & \vdots \\ \dfrac{\partial u_N}{\partial u_1} & \dfrac{\partial u_N}{\partial u_2} & \cdots & \dfrac{\partial u_N}{\partial u_{N-1}} & 1 \end{pmatrix}. \tag{70}$$

To summarize, the essence of the calculations of the forward and the adjoint/reverse modes is shown in the following diagram:

Forward Mode		Adjoint/Reverse Mode
$\dfrac{du_1}{dp} \to \dfrac{du_2}{dp} \to \cdots \to \dfrac{du_N}{dp} \to \dfrac{du}{dp}$	vs.	$\dfrac{\partial u}{\partial u_N} \to \dfrac{\partial u}{\partial u_{N-1}} \to \cdots \to \dfrac{\partial u}{\partial u_1} \to \dfrac{du}{dp}$

For those readers who need more detail on the theory, implementation, software, and generalizations see [25]. One cautionary note is in order: the input and output variables *must* be independent variables; only the intermediate variables can be dependent.

Input Variables	Intermediate Variables	Output Variables
$u_{-K}, \ldots, u_{-2}, u_1$	$u_1, u_2, \ldots, u_M$	$u_{M+1}, u_{M+2}, \ldots, u_{M+L}$
Independent	Dependent	Independent

8 Optimization Problems

A major objective of epidemiology is to identify and quantify the relevant mechanisms that determine how a disease propagates through a susceptible population. This information can be used to develop intervention strategies that will effectively and efficiently minimize the outbreak and the subsequent deleterious effects. Inherent in the decision-making process is the fact that resources used to intervene, such as money, vaccines, antibiotics, trained medical personnel, isolation, diagnosis using syndromic surveillance, etc., are limited. Determining what the optimal strategy should be, and how to implement such a strategy, is not a trivial matter. In

[5] For those readers who want more details on the theory and implementation of AD see [25].

this section we discuss two commonly occurring optimization problems from the decision-making sciences, namely the linear and quadratic programming problems. Additionally, we introduce an optimization/control problem in the context of an influenza pandemic.

8.1 Linear Programming Problem: BVD Disease

In the realm of veterinary epidemiology, bovine viral diarrhoea (BVD) [20] has, and will continue to have, a significant economic impact on the farming industry. Since this is such a competitive market, any losses caused by the disease must be balanced with the associated costs of eradication, prevention and treatment strategies. For example, replacement of the breeding stock will change the age structure of the herd. This strategy affects the productivity of the herd and disease outbreak.

In light of these and many other practical aspects, it may be more realistic to examine the economic options available to the farmer, which will have direct consequences on the epidemiology of the spread of BVD, rather than modeling the disease as an outbreak in isolation. In other words the economically motivated actions taken by the farmer has significant implications for the epidemiology of the disease and the bottom line. This viewpoint provides farm management with quantitative information about the potential variability in income and hence a measure of potential economic risk.

For this application, the constraints take on a wide range of aspects such as total land area, silage area, silage consumption by cows and heifers, calving rates, subsidies, labor rates, available capital, etc.. Decisions that affect the size and quality of the herd, and the spread of disease include how many female or male calfs are sold, how much graze land is used, number of replacement heifers, double fencing of pastures, vermin control, etc.. Since the primary motivation for any business is profit, financial aspects are of primary concern to management. However, it is well known that there is an associated risk in trying to maximize profit, as is easily demonstrated by the stock market. A whole-farm business model [11] in this context would quantify the cost of disease intervention strategies verses the variability of income. Furthermore, a SA of the optimal solution, wrt. the constraints and limited resources, would give quantitative information about which aspects have the most/least effect on the risk and a cost-benefit analysis.

A commonly used methodology in the decision-making sciences is to formulate this problem as a linear programming problem (LPP) [31]. The essential components of a LPP are (1) an objective function which is to be minimized (e.g. cost, risk, etc.,) or maximized (e.g. profit, productivity, etc.,) and (2) constraints (limited resources such as money, silage land, etc.).

Definition 1 (Standard/Forward/Primal LPP). *Let $u_1, u_2, \ldots, u_n$ denote the individual production levels of n commodities with associated unit profits $c_1, c_2, \ldots, c_n$. Let a_{ij} denote the unit amount of resource b_i consumed in the production of commodity j. The* ***Standard/Forward/Primal LPP*** *is defined as*

Maximize the profit function

$$J(u_1, u_2, \ldots, u_n) := c_1 u_1 + c_2 u_2 + \cdots + c_n u_n = \boldsymbol{c}^T \boldsymbol{u},$$

subject to the linear inequality constraints

$$\begin{aligned} a_{11}u_1 + a_{12}u_2 + \cdots + a_{1n}u_n &\le b_1 \\ a_{21}u_1 + a_{22}u_2 + \cdots + a_{2n}u_n &\le b_2 \\ &\vdots \\ a_{m1}u_1 + a_{m2}u_2 + \cdots + a_{mn}u_n &\le b_m \\ u_1, u_2, \cdots, u_m &\ge 0, \end{aligned}$$

or in matrix form, the constraints are written as $\boldsymbol{Au} \le \boldsymbol{b}$.

It is standard practice to assume that the parameters a_{ij}, b_i and c_j are nonnegative. When this is not the case, then usually a simple change of variables can map the original parameters to a situation where it is true.

Sensitivity analysis allows the analyst a way to determine which of the parameters a_{ij}, b_i, or c_j, defining the problem, has the most effect on the profit function. Since we are interested in how the profit function is affected by perturbations to the defining parameters, we must explicitly find the derivative of the profit function, wrt. changes in the defining parameters. Let p denote any of the parameters a_{ij}, b_i, or c_j, in which case we wish to find

$$\frac{\partial J}{\partial p} = \mathbf{c}^T \frac{\partial \mathbf{u}}{\partial p} + \frac{\partial \mathbf{c}^T}{\partial p}\mathbf{u}. \tag{71}$$

Although rarely discussed, the associated adjoint or dual problem is crucial in finding the sensitivity of the profit function. The main difficulty is in evaluating the derivative expression $\mathbf{c}^T \partial \mathbf{u}/\partial p$ term. To eliminate this problem, the associated adjoint/dual problem will naturally occur, in which case a derivative does not need to be explicitly calculated. Instead, we only need to obtain the solutions to the forward and adjoint/dual problems. Since the simplex method produces both solutions simultaneously, no extra calculations are needed. For completeness, recall the associated adjoint/dual LPP:

Definition 2 (Adjoint/Dual LPP). *The **Adjoint/Dual LPP** is defined as*

Minimize the cost function

$$J(v_1, v_2, \ldots, v_m) := b_1 v_1 + b_2 v_2 + \cdots + b_m v_m = \boldsymbol{b}^T \boldsymbol{v},$$

subject to the inequality constraints

$$\begin{aligned} a_{11}v_1 + a_{21}v_2 + \cdots + a_{m1}v_m &\geq c_1 \\ a_{12}v_1 + a_{22}v_2 + \cdots + a_{m2}v_m &\geq c_2 \\ &\vdots \\ a_{1n}v_1 + a_{2n}v_2 + \cdots + a_{mn}v_m &\geq c_n \\ v_1, v_2, \cdots, v_m &\geq 0, \end{aligned}$$

or in matrix form $\boldsymbol{A}^T\boldsymbol{v} \geq \boldsymbol{c}$.

Sensitivity of the Parameter Space

Many of the commonly occurring optimization problems can be written in the form

Maximize/Minimize a given objective function

$$J(\mathbf{u}) = F(u_1, \ldots, u_n)$$

subject to the K equality and L inequality constraints

$$\begin{aligned} f_k(\mathbf{u}) &= 0 \qquad \text{where} \quad k = 1, \ldots, K \\ g_l(\mathbf{u}) &\leq 0 \qquad \text{where} \quad l = 1, \ldots, L. \end{aligned}$$

To determine the sensitivity of the profit function to perturbations in the parameters, we form a modified Lagrange function based on the Karush-Kuhn-Tucker (KKT) theorem [17]. Recall from multivariable calculus that the technique of the method of Lagrange multipliers was used to find the maximum/minimum of a given function, subject to specified *equality* constraints. In the field of optimization, there exists an analogous method when a mixture of equality and inequality constraints are present.

The procedure is based on a modified Lagrangian function, which is a result of the KKT theorem. In applying this theorem, an adjoint problem naturally arises. This modified Lagrangian function is constructed by forming a linear combination of the objective functional and the constraints as

$$\mathcal{L}(\mathbf{u}; \mu, \lambda) := F(\mathbf{u}) + \sum_{k=1}^{K} \mu_k f_k(\mathbf{u}) + \sum_{l=1}^{L} \lambda_l g_l(\mathbf{u}), \tag{72}$$

where μ_k and λ_l are called the Lagrange multipliers. as we shall see, the Lagrange multipliers are in fact adjoint variables.

Theorem 1 (Karush/Kuhn/Tucker Theorem). *An optimal solution is found by solving the associated equations*

$$\frac{\partial F(\boldsymbol{u}^*)}{\partial u_j} + \sum_{k=1}^{K} \mu_k \frac{\partial f_k(\boldsymbol{u}^*)}{\partial u_j} + \sum_{l=1}^{L} \lambda_l \frac{\partial g_l(\boldsymbol{u}^*)}{\partial u_j} = 0 \qquad \textit{for} \quad j = 1, \ldots n$$

$$\mu_k f_k(\boldsymbol{u}^*) = 0, \qquad \textit{for} \quad k = 1, \ldots L$$

$$\lambda_l g_l(\boldsymbol{u}^*) = 0, \qquad \textit{for} \quad l = 1, \ldots L$$

where $\boldsymbol{u}^*$ *is optimal in the sense that* $F(\boldsymbol{u}^*) \leq F(\boldsymbol{u})$*, where* $\boldsymbol{u}$ *is any admissible solution.*

We begin by changing the linear inequality constraints in the forward problem into equality constraints by introducing slack variables $s_1, s_2, \ldots, s_m$ as follows:

$$\begin{aligned}
a_{11}u_1 + a_{12}u_2 + \cdots + a_{1n}u_n + (s_1)^2 &= b_1 \\
a_{21}u_1 + a_{22}u_2 + \cdots + a_{2n}u_n + (s_2)^2 &= b_2 \\
&\vdots \\
a_{m1}u_1 + a_{m2}u_2 + \cdots + a_{mn}u_n + (s_m)^2 &= b_m \\
u_1, u_2, \cdots, u_m &\geq 0.
\end{aligned}$$

Notice that we have deviated from the usual procedure of introducing nonnegative slack variables as $(s_i)^2$ rather than just s_i.

To apply the KKT theorem, we next construct the associated Lagrange function

$$\begin{aligned}
\mathcal{L} := {} & c_1u_1 + c_2u_2 + \cdots c_nu_n \\
& + v_1\left(b_1 - a_{11}u_1 - a_{12}u_2 - \cdots - a_{1n}u_n - (s_1)^2\right) \\
& + v_2\left(b_2 - a_{21}u_1 - a_{22}u_2 - \cdots - a_{2n}u_n - (s_2)^2\right) \\
& \vdots \\
& + v_m\left(b_m - a_{m1}u_1 - a_{m2}u_2 - \cdots - a_{mn}u_n - (s_m)^2\right),
\end{aligned}$$

where the v_i are called the Lagrange multipliers. Using the usual inner product notation, the Lagrange function can be written in the more concise form

$$\mathcal{L} := \mathbf{c}^T\mathbf{u} + \mathbf{v}^T\left(\mathbf{b} - \mathbf{A}\mathbf{u} - \begin{pmatrix} (s_1)^2 \\ (s_2)^2 \\ \vdots \\ (s_m)^2 \end{pmatrix}\right).$$

The optimal solution occurs at a critical point of the Lagrange function, that is, when the system of equations

$$\frac{\partial \mathcal{L}}{\partial u_j} = 0, \qquad \frac{\partial \mathcal{L}}{\partial s_i} = 0, \qquad \text{and} \qquad \frac{\partial \mathcal{L}}{\partial v_i} = 0$$

are satisfied. These equations respectively reduce to the adjoint problem:

$$\mathbf{A}^T \mathbf{v} = \mathbf{c}, \tag{73}$$

the orthogonality conditions:

$$v_i s_i = 0, \qquad \text{for} \quad i = 1, \ldots m, \tag{74}$$

and lastly to the forward problem:

$$\mathbf{A}\mathbf{u} + \begin{pmatrix} (s_1)^2 \\ (s_2)^2 \\ \vdots \\ (s_m)^2 \end{pmatrix} = \mathbf{b}. \tag{75}$$

Taking the transpose of the adjoint problem given in Equation (73) and substituting into the derivative of the profit function given in Equation (71) gives

$$\frac{\partial J}{\partial p} = \mathbf{v}^T \mathbf{A} \frac{\partial \mathbf{u}}{\partial p} + \frac{\partial \mathbf{c}^T}{\partial p} \mathbf{u}. \tag{76}$$

To evaluate this expression, we must somehow evaluate the derivative $\partial \mathbf{u}/\partial p$. We will circumvent this problem by relating this derivative with the adjoint solution $\mathbf{v}$. To obtain this relationship, differentiate the forward problem given in Equation (75) wrt. the parameter p to get

$$\mathbf{A}\frac{\partial \mathbf{u}}{\partial p} + \frac{\partial \mathbf{A}}{\partial p}\mathbf{u} + 2 \begin{pmatrix} s_1 \frac{\partial s_1}{\partial p} \\ s_2 \frac{\partial s_2}{\partial p} \\ \vdots \\ s_m \frac{\partial s_m}{\partial p} \end{pmatrix} = \frac{\partial \mathbf{b}}{\partial p}.$$

Now premultiply by $\mathbf{v}^T$ and use the orthogonality conditions given in Equation (74) to obtain

$$\mathbf{v}^T \mathbf{A} \frac{\partial \mathbf{u}}{\partial p} = \mathbf{v}^T \left(\frac{\partial \mathbf{b}}{\partial p} - \frac{\partial \mathbf{A}}{\partial p} \mathbf{u} \right),$$

in which case

$$\begin{aligned}\frac{\partial J}{\partial p} &= \mathbf{v}^T \mathbf{A} \frac{\partial \mathbf{u}}{\partial p} + \frac{\partial \mathbf{c}^T}{\partial p}\mathbf{u} \\ &= \mathbf{v}^T \left(\frac{\partial \mathbf{b}}{\partial p} - \frac{\partial \mathbf{A}}{\partial p}\mathbf{u} \right) + \frac{\partial \mathbf{c}^T}{\partial p}\mathbf{u}.\end{aligned}$$

The utility of this formula is that to calculate $\partial J/\partial p$, only static/fixed quantities need to be known, specifically the solutions to the forward and adjoint problems, namely $\mathbf{u}$ and $\mathbf{v}$. Since the simplex method calculates both solutions simultaneously, there is no need to make perturbations to the simplex tableau, and reapply the simplex method for each change.

For the cases where $p = b_i$, $p = a_{ij}$, or $p = c_j$ the respective derivatives reduce to

$$\frac{\partial J}{\partial b_i} = v_i \qquad \text{for} \quad i = 1, \ldots, m,$$

$$\frac{\partial J}{\partial a_{ij}} = -v_i u_j \qquad \text{for} \quad i = 1, \ldots, m, \quad \text{and} \quad j = 1, \ldots, n, \qquad \text{and}$$

$$\frac{\partial J}{\partial c_j} = u_j \qquad \text{for} \quad j = 1, \ldots, n.$$

Notice that $\partial J/\partial b_i$ and $\partial J/\partial c_j \geq 0$, while $\partial J/\partial a_{ij} \leq 0$. This means that as the limited resources b_i, or unit profits c_j are increased, the profit is increased, whereas if the unit consumption quantities a_{ij} are increased, the profit is decreased, as is expected.

8.2 Quadratic Programming Problem: Wheat Selection

In 1952, Harry Markowitz [24] published a seminal paper titled "Portfolio Selection" which laid the foundation for what is now called modern portfolio theory. Markowitz constructed the mathematical framework for the well known and accepted observation that investors, although seeking a maximum return on their investments, also simultaneously want to minimize the associated risk. What his work espoused was that the proper mixture of various investments can significantly reduce the overall volatility of the portfolio, while maintaining a "high" rate of return. More precisely, Markowitz was able to quantitatively provide two solutions: a maximum amount of return for a given level of risk, or a minimum level of risk for a given amount of return.

Since cereal grains, such as wheat, provide a substantial portion of the caloric needs of humans worldwide, issues such as disease management and prevention are of the utmost importance. In the United States, Kansas is the leading wheat grower in the nation, and is acutely aware of the effects of soil type, average rainfall, disease tolerance, etc., on the yield, and hence the bottom line. To further complicate the

problem, agricultural researchers are attempting to produce perennial grain crops that will displace the annual crops that are currently planted. The commonly used practices, that reduce disease inoculum in annual crops, such as tillage, delayed planting, or crop rotation, are not applicable to perennial crops. In this situation, farmers would need to plant blends of seeds from a mixture of cultivars (varieties). This strategy of using mixtures of cultivars has been shown to be effective in the management/prevention of disease.

In the jargon of modern portfolio theory, investment in securities, stocks or bonds is replaced with the planting of multiple wheat cultivars. The objective of maximizing the expected rate of return on the investments is replaced with maximizing the wheat yield. Finally, minimize the financial risks is replaced by minimizing the variation in wheat yield due to "genotype-environment interaction," that is, how each cultivar responds to the inevitable unpredictable environmental conditions. Once quantitative values can be established for the average yield, and the variance and covariance of yields of each cultivar, an optimal portfolio is found by solving a Quadratic Programming Problem (QPP) [6].

In the case of modern portfolio theory, risk is defined in terms of the standard deviation/variance of the return on the assets, and is in fact a quadratic functional. Since the risk in the wheat portfolio is also a function of the variance, this problem will also be a QPP. Lastly, a SA of the optimal solution(s) provides quantitative information on which aspects have the most effect on the optimal solution(s).

Definition 3 (Quadratic Programming Problem QPP). *The Quadratic Programming Problem (QPP) is defined as*

Maximize the profit function

$$J(u_1, u_2, \ldots, u_n) := \boldsymbol{c}^T \boldsymbol{u} - \frac{1}{2}\boldsymbol{u}^T \boldsymbol{Q}\, \boldsymbol{u},$$

subject to the linear inequality constraints

$$\begin{aligned} a_{11}u_1 + a_{12}u_2 + \cdots + a_{1n}u_n &\leq b_1 \\ a_{21}u_1 + a_{22}u_2 + \cdots + a_{2n}u_n &\leq b_2 \\ &\vdots \\ a_{m1}u_1 + a_{m2}u_2 + \cdots + a_{mn}u_n &\leq b_m \\ u_1, u_2, \cdots, u_m &\geq 0, \end{aligned}$$

or in matrix form, the constraints are written as $\boldsymbol{A}\boldsymbol{u} \leq \boldsymbol{b}$.

[6] For the general LPP discussed earlier, it is assumed that the profit function is strictly linear in terms of the production level of the associated products. Intuitively this assumption cannot hold true for arbitrary levels of production. One would expect that if the level of production was sufficiently high, the profit would decrease. A common way of incorporating this behavior into the model is to subtract a quadratic term from the objective function. In essence, the quadratic expression can be thought of as a penalty function for excessive production [3, 4].

The matrix $\mathbf{Q}$ is assumed to be a symmetric, positive semi-definite matrix; it is sometimes referred to as the Hessian matrix. The expression $(1/2)\mathbf{u}^T\,\mathbf{Q}\,\mathbf{u}$ is a quadratic form and represents the penalty of excess production.

8.2.1 Sensitivity of the Parameter Space

As was done in the LPP, the inequality constraints are transformed into equality constraints by the introduction of slack variables, as given in Equation (75). To apply the Karush-Kuhn-Tucker theorem, construct the extended Lagrange function

$$\mathcal{L} := \mathbf{c}^T\mathbf{u} - \frac{1}{2}\mathbf{u}^T\,\mathbf{Q}\,\mathbf{u} + \mathbf{v}^T\left(\mathbf{b} - \mathbf{A}\mathbf{u} - \begin{pmatrix}(s_1)^2\\(s_2)^2\\\vdots\\(s_m)^2\end{pmatrix}\right).$$

Once again, the optimal solution occurs at a critical point of the Lagrange function, that is, when the system of equations

$$\frac{\partial\mathcal{L}}{\partial u_j} = 0, \qquad \frac{\partial\mathcal{L}}{\partial s_i} = 0, \qquad \text{and} \qquad \frac{\partial\mathcal{L}}{\partial v_i} = 0$$

are satisfied. These equations respectively reduce to the nonhomogeneous adjoint problem:

$$\mathbf{A}^T\mathbf{v} = \mathbf{c} - \mathbf{Q}\mathbf{u}, \tag{77}$$

the orthogonality conditions given in Equation (74), and lastly to the forward problem given in Equation (75). Notice that if the matrix $\mathbf{Q}$ is the zero matrix, then the nonhomogeneous adjoint problem for the QPP reduces to the homogeneous adjoint problem for the LPP, as is to be expected.

Let p denote any of the parameters a_{ij}, b_i, c_j, or q_{ij}, where q_{ij} denotes the i, j entry of the matrix $\mathbf{Q}$. Next, differentiate the cost function, wrt. parameter p:

$$\frac{\partial J}{\partial p} = \frac{\partial\mathbf{c}^T}{\partial p}\mathbf{u} - \frac{1}{2}\mathbf{u}^T\frac{\partial\mathbf{Q}}{\partial p}\mathbf{u} + \frac{1}{2}\left(2\mathbf{c}^T\frac{\partial\mathbf{u}}{\partial p} - \mathbf{u}^T\mathbf{Q}\frac{\partial\mathbf{u}}{\partial p} - \frac{\partial\mathbf{u}^T}{\partial p}\mathbf{Q}\mathbf{u}\right). \tag{78}$$

Since the matrix $\mathbf{Q}$ is symmetric, then

$$\left(\mathbf{Q}\frac{\partial\mathbf{u}}{\partial p}\right)^T = \frac{\partial\mathbf{u}^T}{\partial p}\mathbf{Q},$$

in which case Equation (78) reduces to

$$\frac{\partial J}{\partial p} = \frac{\partial\mathbf{c}^T}{\partial p}\mathbf{u} - \frac{1}{2}\mathbf{u}^T\frac{\partial\mathbf{Q}}{\partial p}\mathbf{u} + \left(\mathbf{c}^T - \mathbf{u}^T\mathbf{Q}\right)\frac{\partial\mathbf{u}}{\partial p}.$$

The last expression in this equation contains the derivative term $\partial \mathbf{u}/\partial p$ and will be replaced by an expression containing the forward and adjoint solutions. This expression is found by differentiating the forward problem given in Equation (75).

Next, premultiply this result by the modified adjoint solution $\mathbf{v}^T$, and lastly use the orthogonality conditions given in Equation (74). Specifically,

$$\begin{aligned}\mathbf{v}^T \mathbf{A} \frac{\partial \mathbf{u}}{\partial p} &= \left(\mathbf{c}^T - \mathbf{u}^T \mathbf{Q}\right) \frac{\partial \mathbf{u}}{\partial p} \\ &= \mathbf{v}^T \left(\frac{\partial \mathbf{b}}{\partial p} - \frac{\partial \mathbf{A}}{\partial p}\mathbf{u}\right),\end{aligned}$$

in which case

$$\frac{\partial J}{\partial p} = \mathbf{v}^T \left(\frac{\partial \mathbf{b}}{\partial p} - \frac{\partial \mathbf{A}}{\partial p}\mathbf{u}\right) + \frac{\partial \mathbf{c}^T}{\partial p}\mathbf{u} - \underbrace{\frac{1}{2}\mathbf{u}^T \frac{\partial \mathbf{Q}}{\partial p}\mathbf{u}}_{\text{Additional Term}} . \tag{79}$$

Notice that only the solutions to the forward and adjoint problems are needed to find the derivative of the objective function.

Comparing this result with the LPP, if the matrix $\mathbf{Q}$ is the zero matrix then the QPP reduces to the LPP as expected. For the parameters a_{ij}, b_i, and c_j, the derivatives $\partial J/\partial a_{ij}$, $\partial J/\partial b_i$, and $\partial J/\partial c_j$ are the same form as given for the LPP. However, it should be noted that the adjoint solution $\mathbf{v}$ of Equation (77) is not the same as in the LPP.

8.3 Adjoint Operator, Problem, and Sensitivity

This section provides the generalization for constructing the adjoint problem in its most powerful form. The crucial requirements to take note of are:

- there must be a natural way to define an inner product on the FSE
- the associated adjoint problem must provide a way to allow a natural evaluation of the derivative $\partial \mathbf{u}/\partial p$, or some functional $J(\mathbf{u})$.

The following sketch [19, 20] provides an overview of how the generalized adjoint problem is constructed. The types of problems which are amenable to the adjoint methodology are those that can be expressed in the form

$$F(u) = f,$$

where F is a linear/nonlinear operator $F : X \to Y$, and f is the forward forcing function. The domain and range X and Y are assumed to have sufficiently nice topological properties. For example, both X and Y could be Hilbert or Sobolov spaces. Also, associated with the forward problem is the task of determining the sensitivity of some desired response function(al) $J(u)$.

The adjoint problem arises naturally by the introduction of an adjoint variable $v \in X$, through the calculation of the Gâteaux derivative:

$$F'(u)v := \lim_{\epsilon \to 0} \frac{F(u + \epsilon v) - F(u)}{\epsilon}.$$

This definition can be thought of as a directional derivative of the operator F at the point u, and in the direction of the adjoint variable v. The somewhat awkward notation $F'(u)v$ is intended to suggest that the operator F takes the forward variable u, and maps it to an operator F', which now depends on both u and the adjoint variable v.

The next piece of necessary machinery is to formulate an extended representation of the operator F. This is accomplished by assuming that F is sufficiently Gâteaux differentiable. Application of the intermediate-value theorem of operators, about the point u_0, permits us to rewrite the forward operator F in extended form:

$$\Phi(u)u = F(u),$$

where the operator Φ is defined in integral form

$$\Phi(u)v := F(u_0) + \int_{\tau=0}^{1} F'(u_0 + \tau(u - u_0))\, d\tau (v - u_0),$$

Given that an appropriate inner product has been defined, consider the adjoint operation

$$\langle \Phi(u)v, w \rangle = \text{SC1} + \langle v, \Phi^{\dagger}(u)w \rangle,$$

where SC1 denotes the 1st solvability condition, and $\Phi^{\dagger}$ denotes the adjoint operator associated with the forward operator Φ. When SC1 = 0, the result is referred to as the Lagrange identity. The associated generalized adjoint problem is defined as

$$\Phi^{\dagger}(u)v = g,$$

where the adjoint forcing function g has not yet been specified. As was illustrated in the linear system problem, not specifying g at this time is advantageous, since it may be cleverly related to the response functional J.

A second solvability condition SC2 occurs when the forward and adjoint problems are related. Assuming that the Lagrange identity is satisfied, i.e. SC1 = 0, then taking the dot product of the forward problem with the adjoint solution gives

$$\langle \Phi(u)u, v \rangle = \langle f, v \rangle,$$

while taking the dot product of the adjoint problem with the forward solution gives

$$\begin{aligned}\langle \Phi^{\dagger}(u)v, u\rangle &= \langle g, u\rangle \\ \langle v, \Phi(u)u\rangle &= \langle g, u\rangle \\ \langle v, f\rangle &= \langle g, u\rangle.\end{aligned}$$

This invariance condition, or second solvability condition SC2, relates the forward and adjoint solutions and forcing functions by

$$\langle g, u\rangle = \langle f, v\rangle.$$

Finally, the adjoint forcing function g is cleverly chosen so that

$$\langle g, u\rangle = J(u).$$

We summarize the construction of the adjoint problem in the following diagram (see Fig. 9 below):

For the linear system, the adjoint methodology produces the result that the adjoint problem is $\mathbf{A}^T\mathbf{v} = \mathbf{c}$, provided the operator equation $F(\mathbf{u}) = f$ is constructed from the forward sensitivity equation. Specifically, the results follow when

$$F(\mathbf{u}) := \mathbf{A}\frac{\partial \mathbf{u}}{\partial q} + \frac{\partial \mathbf{A}}{\partial q}\mathbf{u}, \qquad f := \frac{\partial \mathbf{b}}{\partial q},$$
$$\text{and} \qquad J(\mathbf{u}) := \left\langle \frac{\partial \mathbf{u}}{\partial q}, \mathbf{c} \right\rangle.$$

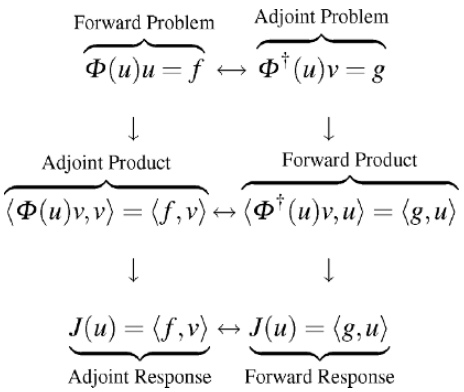

Fig. 9 Construction of the Adjoint Problem

9 Examples

In this section we highlight a warning: "Let the buyer beware!" The warnings are a discussion of some of the pitfalls/shortcomings that can occur in FSA and ASA. Here we list situations where the reader should proceed with caution:

- In order for an adjoint problem to be defined, an associated inner product structure must exist. **No inner product $\Longrightarrow$ No adjoint**.
- To determine the sensitivity of the associated functional $J = J(u)$, using the adjoint methodology, the functional must be cleverly written in terms of the inner product.
- Once an adjoint problem has been defined, if more than one sensitivity is required, (e.g., recall the case of the sensitivity of the eigenvalues and eigenvectors), additional information must be introduced to make further progress.
- SA as discussed here is local in nature. The estimates of derivatives are valid only in some "small" neighborhood of the specified nominal values of the parameters. For a more global approach, uncertainty quantification methodology should be used.

In the following examples we provide some insight into how one might attain explicit formula for derivatives of aspects of solutions, which cannot be defined in terms of an inner product. The basic tool is not exotic, rather ubiquitous: the chain rule. As another disclaimer, the following examples are provided in the hopes that they might be useful in your program of SA, and stimulate ideas that would allow you to build additional tools of SA in your own specific realm of research.

9.1 Sensitivity of the Doubling Time

Suppose we have an IVP and we are interested in the time it takes for the solution $u = u(t)$ to double its initial value, i.e., $u(t_D) = 2u_0$. For example, we might wish to know the doubling time for the number of people infected in an epidemic and how it it affected by changes to specific parameters. The typical difficulty is that, in general, we do not have the explicit forward solution, in which case explicit expressions for the desired derivatives are not available. However, numerical values for these derivatives can be calculated using the numerical solution of the forward sensitivity equation(s). The derivatives of interest are found by application of the following lemma.

Lemma 1 (Sensitivity of time to attain a multiple of the initial condition). *Let $u = u(t; p, u_0)$ be the solution to the first order IVP*

$$\frac{du}{dt} = f(u, t; p) \qquad with \qquad u(0) = u_0, \tag{80}$$

where f is differentiable in u, t, and p. Let t_k denote the time t for which u attains the value $u(t_k) = ku_0$, where $k > 0$. The derivative dt_k/dp is given by

$$\frac{dt_k}{dp} = -\frac{\left.\dfrac{\partial u}{\partial p}\right|_{t=t_k}}{f(ku_0, t_k; p)}, \tag{81}$$

and dt_k/du_0 is given by

$$\frac{dt_k}{du_0} = -\frac{k - \left.\dfrac{\partial u}{\partial u_0}\right|_{t=t_k}}{f(ku_0, t_k; p)} = 0. \tag{82}$$

Proof. When $t = t_k$ the solution u satisfies the condition $u(t_k) = ku_0$ and upon differentiation wrt. the parameter p, we obtain

$$\left.\frac{d}{dp}\left[u(t; p, u_0)\right]\right|_{t=t_k} = \frac{d}{dp}\left[ku_0\right].$$

Assuming that k and u_0 are independent of the parameter p, this equation reduces to

$$\left.\frac{du}{dt}\right|_{t=t_k}\frac{dt_k}{dp} + \left.\frac{\partial u}{\partial p}\right|_{t=t_k} = 0,$$

and upon solving for $\partial t_k/\partial p$, we obtain the result given in Equation (81). Similarly, differentiate $u_k = ku_0$ wrt. u_0 to get

$$\left.\frac{d}{du_0}\left[u(t; p, u_0)\right]\right|_{t=t_k} = \frac{d}{du_0}\left[ku_0\right].$$

Assuming that k and p are independent of u_0, this equation reduces to

$$\left.\frac{du}{dt}\right|_{t=t_k}\frac{dt_k}{du_0} + \left.\frac{\partial u}{\partial u_0}\right|_{t=t_k} = k.$$

But when $t = t_k$ then $u(t_k) = ku_0$, which means $\partial u/\partial u_0|_{t=t_k} = k$, in which case $dt_k/du_0 = 0$.

9.2 Sensitivity of a Critical Point

An important application of SA is to determine which parameter(s), of an IVP modeling the spread of an epidemic, has the most effect on the peak of the infection. In other words, we want to determine the sensitivity of a critical point, to parameters

or initial conditions. Specifically we must calculate the derivatives $\partial u/\partial p|_{t=t_{\rm cp}}$ and $\partial t/\partial p|_{t=t_{\rm cp}}$ where $t_{\rm cp}$ denotes the time when the solution is at a critical point $u_{\rm cp}$.

Lemma 2 (Sensitivity of Critical Points). *The derivative dt_{cp}/dp is given by*

$$\frac{dt_{cp}}{dp} = -\frac{\left(\dfrac{\partial f}{\partial p} + \dfrac{\partial f}{\partial u}\dfrac{\partial u}{\partial p}\right)\Big|_{t=t_{cp}}}{\left.\dfrac{\partial f}{\partial u}\right|_{t=t_{cp}}}, \tag{83}$$

and $\partial u/\partial p|_{t=t_{cp}}$ is found numerically by solving the FSE

$$\frac{d}{dt}\left[\frac{\partial u}{\partial p}\right] = \frac{\partial f}{\partial u}\frac{\partial u}{\partial p} + \frac{\partial f}{\partial p}. \tag{84}$$

Similarly, the derivative dt_{cp}/dp is given by

$$\frac{dt_{cp}}{du_0} = -\frac{\left.\dfrac{\partial f}{\partial u}\dfrac{\partial u}{\partial u_0}\right|_{t=t_{cp}}}{\left.\dfrac{\partial f}{\partial u}\right|_{t=t_{cp}}}, \tag{85}$$

and $\partial u/\partial u_0|_{t=t_{cp}}$ is found numerically by solving the FSE

$$\frac{d}{dt}\left[\frac{\partial u}{\partial u_0}\right] = \frac{\partial f}{\partial u}\frac{\partial u}{\partial u_0}. \tag{86}$$

Proof. Now a critical point $u_{\rm cp}$ at time $t_{\rm cp}$ satisfies the property that

$$f(u_c, t_c; p) = 0. \tag{87}$$

Differentiating this equation wrt. the parameter p gives the single equation

$$\left.\frac{\partial f}{\partial u}\frac{\partial u}{\partial p}\right|_{t=t_{\rm cp}} + \left.\frac{\partial f}{\partial t}\frac{\partial t}{\partial p}\right|_{t=t_{\rm cp}} + \left.\frac{\partial f}{\partial p}\right|_{t=t_{\rm cp}} = 0. \tag{88}$$

in the two unknowns $\partial u/\partial p|_{t=t_{\rm cp}}$ $\partial t/\partial p|_{t=t_{\rm cp}}$. Solving this equation for $\partial t/\partial p|_{t=t_{\rm cp}}$ and numerically solving the above mentioned FSE for $\partial u/\partial p|_{t=t_{\rm cp}}$ gives the desired result. The other result is obtained in a similar fashion.

9.3 Sensitivity of Periodic Solutions to Parameters

Consider the IVP where the forward solution u approaches a limit cycle of period $\mathcal{T}$ as $t \to \infty$. As is almost aways the case, a closed form of the forward solution is not available, in which case the derivative $\partial\mathcal{T}/\partial p$ can not be explicitly obtained.

As seen from the previous examples, the key to obtaining the desired derivative is to state, mathematically, the desired property, apply the chain rule, and possibly utilize the solution to the FSEs. In this example, the key observation is that if u is periodic with period $\mathcal{T}$, where $t \in [0, \infty)$, u_0 and $u_0{}'$ are given initial conditions, and p is a parameter, then

$$u(t + \mathcal{T}; u_0, u_0{}', p) = u(t; u_0, u_0{}', p), \qquad \forall t \in [0, \infty).$$

We will differentiate this expression wrt. the parameter p and find a numerical expression for $d\mathcal{T}/dp$, in terms of the forward sensitivity derivatives. The following lemma gives the desired expressions.

Lemma 3 (Sensitivity of a periodic function). *Let $u = u(t; u_0, u_0{}', p)$ be a family of periodic functions with period $\mathcal{T}$, that is,*

$$u(t + \mathcal{T}; u_0, u_0{}', p) = u(t; u_0, u_0{}', p), \tag{89}$$

$\forall t \in [0, \infty)$ and where u is differentiable in t, u_0, $u_0{}'$, and p. The derivative of the period $\mathcal{T}$ with respect to the parameter p is given by

$$\frac{d\mathcal{T}}{dp} = \frac{\dfrac{\partial u(t; u_0, u_0{}', p)}{\partial p} - \left.\dfrac{\partial u(s; u_0, u_0{}', p)}{\partial p}\right|_{s=t+\mathcal{T}}}{\dfrac{du(t; u_0, u_0{}', p)}{dt}}. \tag{90}$$

The astute reader is no doubt immediately suspicious of this result, since the left hand side seems to be independent of time, while the right hand side is apparently time dependent. However, this "contradiction" will be addressed shortly.

Proof. Differentiate Equation (89) wrt. the parameter p to get

$$\frac{d}{dp}\left[u(s; u_0, u_0{}', p)\right]\Big|_{s=t+\mathcal{T}} = \frac{d}{dp}\left[u(t; u_0, u_0{}', p)\right],$$

or in expanded form

$$\left.\frac{du(s;u_0,u_0',p)}{ds}\right|_{s=t+\mathcal{T}}\frac{d[t+\mathcal{T}]}{dp}+\left.\frac{\partial u(s;u_0,u_0',p)}{\partial u_0}\right|_{s=t+\mathcal{T}}$$
$$\frac{du_0}{dp}+\left.\frac{\partial u(s;u_0,u_0',p)}{\partial u_0'}\right|_{s=t+\mathcal{T}}\frac{du_0'}{dp}+\left.\frac{\partial u(s;u_0,u_0',p)}{\partial p}\right|_{s=t+\mathcal{T}}$$
$$=\frac{du(t;u_0,u_0',p)}{dt}\frac{dt}{dp}+\frac{\partial u(t;u_0,u_0',p)}{\partial u_0}\frac{du_0}{dp}$$
$$+\frac{\partial u(t;u_0,u_0',p)}{\partial u_0'}\frac{du_0'}{dp}+\frac{\partial u(t;u_0,u_0'p)}{\partial p}. \tag{91}$$

Since t, u_0, and u_0' are independent of p, then $dt/dp = du_0/dp = du_0'/dp = 0$, in which case this equation reduces to

$$\left.\frac{du(s;u_0,u_0',p)}{ds}\right|_{s=t+\mathcal{T}}\frac{d\mathcal{T}}{dp}+\left.\frac{\partial u(s;u_0,u_0',p)}{\partial p}\right|_{s=t+\mathcal{T}}=\frac{\partial u(t;u_0,u_0',p)}{\partial p}.$$

Now solve for $d\mathcal{T}/dp$ and use the fact that since u is periodic in t, then

$$\left.\frac{du(s;u_0,u_0',p)}{ds}\right|_{s=t+\mathcal{T}}=\frac{du(t;u_0,u_0',p)}{dt},$$

to obtain the result stated as Equation (89).

A cautionary note is needed to prevent misapplication of this result. The formula given in Equation (89) is for an arbitrary time t as compared to previous examples, where the formula for the derivative of a particular aspect of a problem was valid only at a particular specified point in time. In other words, for a fixed value of the parameter p and initial conditions u_0, and u_0' the expression $d\mathcal{T}/dp$ should remain constant if the period $\mathcal{T}$ is independent of time. That is, we must assume that the periodicity of the solution is not changing, or, at worst, is approaching a fixed value.

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