American Journal of Computational Mathematics, 2020, 10, 355-381
https://www.scirp.org/journal/ajcm
ISSN Online: 2161-1211
ISSN Print: 2161-1203

Illustrative Application of the 2nd-Order Adjoint Sensitivity Analysis Methodology to a Paradigm Linear Evolution/Transmission Model: Point-Detector Response

Dan Gabriel Cacuci

Center for Nuclear Science and Energy, Department of Mechanical Engineering, University of South Carolina, Columbia SC, USA

Email: cacuci@cec.sc.edu

How to cite this paper: Cacuci, D.G. (2020) Illustrative Application of the 2nd-Order Adjoint Sensitivity Analysis Methodology to a Paradigm Linear Evolution/Transmission Model: Point-Detector Response. *American Journal of Computational Mathematics*, **10**, 355-381.
https://doi.org/10.4236/ajcm.2020.103019

Received: May 31, 2020
Accepted: July 19, 2020
Published: July 22, 2020

Abstract

This work illustrates the application of the "Second Order Comprehensive Adjoint Sensitivity Analysis Methodology" (2nd-CASAM) to a mathematical model that can simulate the evolution and/or transmission of particles in a heterogeneous medium. The model response is the value of the model's state function (particle concentration or particle flux) at a point in phase-space, which would simulate a pointwise measurement of the respective state function. This paradigm model admits exact closed-form expressions for all of the 1st- and 2nd-order response sensitivities to the model's uncertain parameters and domain boundaries. These closed-form expressions can be used to verify the numerical results of production and/or commercial software, e.g., particle transport codes. Furthermore, this paradigm model comprises many uncertain parameters which have relative sensitivities of identical magnitudes. Therefore, this paradigm model could serve as a stringent benchmark for inter-comparing the performances of all deterministic and statistical sensitivity analysis methods, including the 2nd-CASAM.

Keywords

Second-Order Adjoint Comprehensive Sensitivity Analysis Methodology (2nd-CASAM), Evolution Benchmark Model, Exact and Efficient Computation of First- and Second-Order Response Sensitivities

1. Introduction

The application of the general second-order adjoint sensitivity analysis methodology presented in [1] is illustrated in this work by means of a simple mathematical model which expresses a conservation law of the model's state function. This paradigm model is representative of transmission of particles and/or radiation through materials [2] [3], chemical kinetics processes [4] [5], radioactive decay modeled by the Bateman equation, etc.

Although the model is simple, it comprises a large number of model parameters, thereby involving a correspondingly large number of sensitivities (*i.e.*, functional derivatives) of the model's responses to the model parameters. Furthermore, the model has been deliberately designed so that a large number of relative response sensitivities display identical values. The fact that the model has a large number of parameters and the fact that all but a few relative sensitivities have identical values would make it very difficult, if not impossible, to use statistical methods to compute the first- and second-order sensitivities of the responses to all of the parameters of this model, since the computational costs would be prohibitive. Of course, statistical methods would not be able to compute the *exact* values of these first- and second-order sensitivities. For such models, involving many parameters but relatively few responses, the Second-Order Comprehensive Adjoint Sensitivity Analysis Methodology (2^{nd}-CASAM) for Linear Systems, presented in Part I [1], is best suited for computing exactly and efficiently the first- and second-order response sensitivities.

This work is organized as follows: Section 2 presents the paradigm evolution model. Section 3 presents the application of the 2^{nd}-CASAM [1] for efficiently computing the exact closed-form expressions of the first-and second-order sensitivities of a "point-type" response to both model and boundary parameters. The concluding remarks offered in Section 4 highlight the comprehensive verification mechanism which is inherently built into the 2^{nd}-CASAM [1] to ensure that the second-level adjoint functions are derived and computed correctly. All in all, the exact expressions of the 1^{st}- and 2^{nd}-order sensitivities presented in this work provide stringent benchmarks for the verification of the accuracies of any other methods, deterministic and/or statistical, for performing sensitivity analysis.

2. Mathematical Modeling of a Paradigm Evolution/Transmission Benchmark Problem

The general 2^{nd}-CASAM methodology presented in [1] is applied in this work to a simple paradigm model, admitting a closed-form analytic solution for convenient verification of all results to be obtained, which simulates a typical evolution or attenuation of a quantity that will be denoted as $\rho(t)$, satisfying the following linear conservation equation:

$$\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}+\rho(t)\sum_{i=1}^{N}n_i\sigma_i=0,\quad 0\le\beta_\ell\le t\le\beta_u<\infty, \tag{1}$$

$$\rho(\beta_\ell)=\rho_{in},\quad \text{at } t=\beta_\ell. \tag{2}$$

The simple evolution system represented by Equations (1) and (2) occurs in the mathematical modeling of many physical systems. $t = t_d$, $0 \le \beta_\ell \le t_d \le \beta_u < \infty$. For example, the dependent variable $\rho(t)$ could represent [2] [3] the evolution of the concentration of a substance in a homogeneous mixture of N materials, from an imprecisely known initial quantity, denoted as ρ_{in}, measured at an initial-time value $t = \beta_\ell$ towards an imprecisely known final-time value $t = \beta_u$. The quantities n_i and σ_i would represent various imprecisely known material (e.g., chemical) properties of the i^{th}-material $(i = 1, \cdots, N)$.

Alternatively, $\rho(t)$ could represent [3] [4] [5] the mono-directional propagation (attenuation) of the flux of uncollided particles (e.g., photons) travelling through a one-dimensional homogenized multi-material slab of imprecisely known thickness $(\beta_u - \beta_\ell)$ in a direction parallel to the t-coordinate. The condition given in Equation (2) would prescribe a beam of particles of imprecisely known intensity ρ_{in} incident on the slab's surface located at the an imprecisely known position $t = \beta_\ell$. Each of the slab's i^{th}-materials $(i = 1, \cdots, N)$ would be characterized by an imprecisely known microscopic cross section σ_i and an imprecisely known atomic number density n_i. Since this work will deliberately focus on illustrating the computation of the response sensitivities to imprecisely known boundaries of a physical system, the possible imprecisely known sources that could appear on the right-side of Equation (1) are not considered, since their inclusion would just complicate the mathematical derivations without bringing any new mathematical or physical insights.

A typical response of interest for the physical problem modeled by Equations (1) and (2) would be a measurement, denoted as $\rho(t_d)$, of $\rho(t)$ at some time instance (or location within the slab or on the slab's surface) $t = t_d$, $0 \le \beta_\ell \le t_d \le \beta_u < \infty$. The following functional, denoted as $R_1(\rho; \boldsymbol{\alpha}, \boldsymbol{\beta})$, can represent mathematically such a measurement:

$$R_1(\rho; \boldsymbol{\alpha}, \boldsymbol{\beta}) \triangleq \int_{\beta_\ell}^{\beta_u} \rho(t) \delta(t - t_d) \mathrm{d}t, \tag{3}$$

where $\delta(t - t_d)$ denotes the well-known Dirac-delta (impulse) functional. In Equation (3), the vector $\boldsymbol{\alpha}$ denotes the "vector of model parameters" and defined as follows:

$$\boldsymbol{\alpha} \triangleq \left(\alpha_1, \cdots, \alpha_{N_\alpha}\right)^\dagger \triangleq \left(n_1, \cdots, n_N, \sigma_1, \cdots, \sigma_N, \rho_{in}, t_d\right)^\dagger. \tag{4}$$

Similarly, the vector $\boldsymbol{\beta}$ denotes the "vector of boundary parameters" and is defined as follows:

$$\boldsymbol{\beta} \triangleq \left(\beta_\ell, \beta_u\right)^\dagger. \tag{5}$$

In Equation (4) and throughout this work, the symbol "$\triangleq$" is used to denote "is defined as" or "is by definition," while the "dagger" $(\dagger)$ superscript is used to denote "transposition."

Although the model parameters ρ_{in}, n_i, σ_i, t_d, Σ_d, together with the boundary parameters β_ℓ and β_u are considered to be imperfectly known and subject to uncertainties, the actual probability distributions of these parameters are not known in practice. Usually, only the "nominal" (or "mean") values and the respective variations from the nominal values (e.g., standard deviations) of the respective components are known. The nominal values will be denoted using the superscript "zero" so that the vector comprising the nominal values of the model parameters, denoted as $\boldsymbol{\alpha}^0$, will be defined for the system under consideration as follows:

$$\boldsymbol{\alpha}^0 \triangleq \left(\alpha_1^0,\cdots,\alpha_{N_\alpha}^0\right)^\dagger \triangleq \left(n_1^0,\cdots,n_N^0,\sigma_1^0,\cdots,\sigma_N^0,\rho_{in}^0,t_d^0\right)^\dagger \tag{6}$$

Similarly, the vector comprising the nominal values of the boundary parameters is denoted as $\boldsymbol{\beta}^0$ and is defined for the system under consideration as follows:

$$\boldsymbol{\beta}^0 \triangleq \left(\beta_\ell^0,\beta_u^0\right)^\dagger. \tag{7}$$

Altogether, the physical system modeled by Equations (1) through (7) comprises 2 boundary parameters and $N_\alpha = 2N+2$ model parameters, which can be a large number for realistic problems. For example, the spent fuel dissolver model analyzed by Cacuci *et al.* (2016), which involves equations similar to Equation (1), comprises $N_\alpha = 1292$ parameters.

For subsequent verification of the expressions that will be obtained for various response sensitivities, the closed-form solution of Equations (1) and (2) is provided below, in Equation (8):

$$\rho(t) = \rho_{in}\exp\left[\left(\beta_\ell - t\right)\sum_{i=1}^{N} n_i\sigma_i\right]. \tag{8}$$

In practice, the nominal solution, denoted as $\rho^0(t)$, is computed by solving numerically Equations (1) and (2) using the nominal values for the model and boundary parameters. For this illustrative example, the nominal solution of Equations (1) and (2) has the following expression:

$$\rho^0(t) = \rho_{in}^0\exp\left[\left(\beta_\ell^0 - t\right)\sum_{i=1}^{N} n_i^0\sigma_i^0\right]. \tag{9}$$

Using Equation (9) in Equation (3) yields the following expression for the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$, which is to be evaluated at the nominal values $\boldsymbol{e}^0 \triangleq \left(\rho^0;\boldsymbol{\alpha}^0,\boldsymbol{\beta}^0\right)$:

$$R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta}) = \left\{\rho_{in}\exp\left[\left(\beta_\ell - t_d\right)\sum_{i=1}^{N} n_i\sigma_i\right]\right\}_{\left(\rho_{in}=\rho_{in}^0,\beta_\ell=\beta_\ell^0,t_d=t_d^0,n_i=n_i^0,\sigma_i=\sigma_i^0\right)}. \tag{10}$$

Of course, the closed-form analytical expression for the problem's dependent variable(s), as provided in Equation (8), and the closed-form expression for the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$, as given in Equation (10), will *not* be available for the large-scale systems encountered in practice. Therefore, the sensitivities (*i.e.*, functional derivatives) of the responses to the model and boundary parameters can only be determined numerically.

3. Application of the 2nd-CASAM for Computing Exactly and Efficiently the 1st- and 2nd-Order Response Sensitivities of a "Point Detector" Response to Uncertain Model and Boundary Parameters

The variations between the true and the nominal values of the model and boundary parameters will be considered to constitute the components of the vectors $\delta\boldsymbol{\alpha}$ and $\delta\boldsymbol{\beta}$, respectively, defined as follows:

$$\delta\boldsymbol{\alpha} \triangleq \left(\delta\alpha_1,\cdots,\delta\alpha_{N_\alpha}\right),\ \ \delta\alpha_i \triangleq \alpha_i - \alpha_i^0, \tag{11}$$

$$\delta\boldsymbol{\beta} \triangleq \left(\delta\beta_\ell,\delta\beta_u\right)^\dagger,\ \ \delta\beta_\ell \triangleq \beta_\ell - \beta_\ell^0,\ \ \delta\beta_u \triangleq \beta_u - \beta_u^0. \tag{12}$$

Since the state function is related to the model and boundary parameters $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ through Equations (1) and (2), it follows that the variations and $\delta\boldsymbol{\beta}$ in the model and boundary parameters will cause a corresponding variation in the state function $\rho(t)$ around the nominal solution $\rho^0(t)$. In turn, these variations will cause variations in the responses $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$ around the respective nominal response values. For subsequent derivations, it is convenient to use the compact notation $\boldsymbol{e} \triangleq (\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$, with the corresponding nominal values denoted as $\boldsymbol{e}^0 \triangleq \left(\rho^0;\boldsymbol{\alpha}^0,\boldsymbol{\beta}^0\right)$.

3.1. Computing the 1st-Order Sensitivities $R_1(\rho;\alpha,\beta)$ Using the 1st-LASS

The total first-order sensitivity of the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta}) \equiv R_1(\boldsymbol{e})$ defined in Equation (3) is provided [6] by the 1st-order total sensitivity (G-differential) $\delta R_1\left(\boldsymbol{e}^0;\delta\rho;\delta\boldsymbol{\alpha},\delta\boldsymbol{\beta}\right)$ evaluated at $\boldsymbol{e}^0 \triangleq \left(\rho^0;\boldsymbol{\alpha}^0,\boldsymbol{\beta}^0\right)$, which is computed by applying the definition of the first-order G-differential to Equation (3), to obtain the following expression:

$$\begin{aligned}
&\delta R_1\left(\boldsymbol{e}^0;\delta\rho;\delta\boldsymbol{\alpha},\delta\boldsymbol{\beta}\right) \\
&\triangleq \frac{\mathrm{d}}{\mathrm{d}\varepsilon}\left\{\int_{\beta_\ell^0+\varepsilon\delta\beta_\ell}^{\beta_u^0+\varepsilon\delta\beta_u}\left[\rho^0(t)+\varepsilon\delta\rho(t)\right]\delta\left(t-t_d^0-\varepsilon\delta t_d\right)\mathrm{d}t\right\}_{\left(\boldsymbol{e}=\boldsymbol{e}^0,\varepsilon=0\right)} \\
&= \left(\delta R_1\right)^{ind} + \left(\delta R_1\right)^{dir},
\end{aligned} \tag{13}$$

where the indirect-effect term $\left(\delta R_1\right)^{ind}$ and, respectively, the direct-effect term $\left(\delta R_1\right)^{dir}$ are defined as

$$\left(\delta R_1\right)^{ind} \triangleq \int_{\beta_\ell^0}^{\beta_u^0}\delta\rho(t)\,\delta\left(t-t_d^0\right)\mathrm{d}t, \tag{14}$$

$$\left(\delta R_1\right)^{dir} \triangleq -\left(\delta t_d\right)\int_{\beta_\ell^0}^{\beta_u^0}\rho^0(t)\,\delta'\left(t-t_d^0\right)\mathrm{d}t = \left(\delta t_d\right)\left\{\frac{\partial\rho(t)}{\partial t}\right\}_{t=t_d^0} \tag{15}$$

The variation $\delta\rho(t)$, of the state function $\rho(t)$, which appears in Equation (14) is the solution of the following First-Level Forward Sensitivity System (1st-LFSS) obtained by G-differentiating Equations (1) and (2) around the nominal parameter values:

$$\frac{\mathrm{d}\left[\delta\rho(t)\right]}{\mathrm{d}t}+\delta\rho(t)\sum_{i=1}^{N}n_i^0\sigma_i^0 = -\rho^0(t)\sum_{i=1}^{N}\left(n_i^0\delta\sigma_i+\sigma_i^0\delta n_i\right),\ 0\le\beta_\ell^0\le t\le\beta_u^0<\infty, \tag{16}$$

$$\delta\rho\left(\beta_\ell^0\right)+\delta\beta_\ell\left\{\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right\}_{t=\beta_\ell^0}=\delta\rho_{in},\ \text{ at } t=\beta_\ell^0. \tag{17}$$

Since the closed-form solution represented by Equation (9) is not available in practice, the direct effect term, $(\delta R_1)^{dir}$, defined by Equation (15) can be computed by differentiating (numerically, in practice) the solution of Equations (1) and (2). Also, in practice, the sensitivities included in the indirect effect, $(\delta R_1)^{ind}$, defined by Equation (14) could be computed only by successively setting all but one of the parameter variations $(\delta\rho_{in},\delta\sigma_i,\delta n_i,\delta\beta_\ell,\delta\beta_u,\delta t_1)$ to zero in the 1st-LFSS [comprising Equations (16) and (17)] and solving numerically the corresponding forms of the resulting 1st-LFSS. Thus, using the 1st-LFSS to compute the sensitivities of the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$ would require $2N+4$ large-scale computations.

The need for performing these $2N+4$ large-scale computations can be avoided by applying the 2nd-CASAM presented in Part I (Cacuci, 2020). In order to apply the 2nd-CASAM, the function $\delta\rho(t)$ is considered to be an element of a Hilbert space $\mathsf{H}^{(1)}(\Omega_t),\Omega_t\triangleq\left(\beta_\ell^0,\beta_u^0\right)$, endowed with the following inner product, denoted as $\langle\rho_1(t),\rho_2(t)\rangle$, between two (square-integrable) functions $\rho_1(t)\in\mathsf{H}^{(1)}(\Omega_t)$ and $\rho_2(t)\in\mathsf{H}^{(1)}(\Omega_t)$:

$$\langle\rho_1(t),\rho_2(t)\rangle\triangleq\int_{\beta_\ell^0}^{\beta_u^0}\rho_1(t)\rho_2(t)\mathrm{d}t. \tag{18}$$

The construction of the requisite First-Level Adjoint Sensitivity System (1st-LASS) commences by multiplying Equation (16) by a square-integrable function $\psi^{(1)}(t)\in\mathsf{H}^{(1)}(\Omega_t)$ and integrating the left-side of the resulting equation by parts once, so as to transfer the differential operation from $\delta\rho(t)$ onto $\psi^{(1)}(t)$. This sequence of steps yields the following relation:

$$\begin{aligned}&\int_{\beta_\ell^0}^{\beta_u^0}\psi^{(1)}(t)\left[\frac{\mathrm{d}\left[\delta\rho(t)\right]}{\mathrm{d}t}+\delta\rho(t)\sum_{i=1}^{N}n_i^0\sigma_i^0\right]\mathrm{d}t\\&=\int_{\beta_\ell^0}^{\beta_u^0}\delta\rho(t)\left[-\frac{\mathrm{d}\psi^{(1)}(t)}{\mathrm{d}t}+\psi^{(1)}(t)\sum_{i=1}^{N}n_i^0\sigma_i^0\right]\mathrm{d}t\\&\quad+\psi^{(1)}\left(\beta_u^0\right)\delta\rho\left(\beta_u^0\right)-\psi^{(1)}\left(\beta_\ell^0\right)\delta\rho\left(\beta_\ell^0\right).\end{aligned} \tag{19}$$

The following sequence of operations is performed next using Equation (19):

1) Require that the first term on the right-side of Equation (19) be identical with the indirect effect $(\delta R_1)^{ind}$ defined in Equation (14).

2) Use the right-side of Equation (16) to replace the term multiplying $\psi^{(1)}(t)$ on the left-side of Equation (19).

3) Eliminate the unknown quantity $\delta\rho\left(\beta_u^0\right)$ on the right-side of Equation (19) by imposing the condition $\psi^{(1)}\left(\beta_u^0\right)=0$.

4) Insert the boundary condition provided in Equation (17) into Equation (19).

The result of the above sequence of operations is the following expression for $\left(\delta R_1\right)^{ind}$:

$$\begin{aligned}\left(\delta R_1\right)^{ind} &= -\sum_{i=1}^{N}\left(n_i^0\delta\sigma_i+\sigma_i^0\delta n_i\right)\int_{\beta_\ell^0}^{\beta_u^0}\psi^{(1)}(t)\rho^0(t)\,\mathrm{d}t \\ &+\psi^{(1)}\left(\beta_\ell^0\right)\left[\delta\rho_{in}-\delta\beta_\ell\left\{\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right\}_{t=\beta_\ell^0}\right],\end{aligned} \tag{20}$$

where the first-level adjoint function $\psi^{(1)}(t)$ appearing in Equation (20) is the solution of the following First-Level Adjoint Sensitivity System (1st-LASS):

$$-\frac{\mathrm{d}\psi^{(1)}(t)}{\mathrm{d}t}+\psi^{(1)}(t)\sum_{i=1}^{N}n_i^0\sigma_i^0=\delta\left(t-t_d^0\right),\ 0\le\beta_\ell^0\le t\le\beta_u^0<\infty, \tag{21}$$

$$\psi^{(1)}\left(\beta_u^0\right)=0 \tag{22}$$

In terms of the first-level adjoint function $\psi^{(1)}(t)$, the partial sensitivities of $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$ with respect to the variations in the model parameters are the quantities in Equation (20) that multiply the respective parameter variations, namely:

$$\left(\frac{\partial R_1}{\partial\sigma_i}\right)_{\boldsymbol{e}^0}=-n_i^0\int_{\beta_\ell^0}^{\beta_u^0}\psi^{(1)}(t)\rho^0(t)\,\mathrm{d}t,\ i=1,\cdots,N, \tag{23}$$

$$\left(\frac{\partial R_1}{\partial n_i}\right)_{\boldsymbol{e}^0}=-\sigma_i^0\int_{\beta_\ell^0}^{\beta_u^0}\psi^{(1)}(t)\rho^0(t)\,\mathrm{d}t,\ i=1,\cdots,N. \tag{24}$$

$$\left(\frac{\partial R_1}{\partial\rho_{in}}\right)_{\boldsymbol{e}^0}=\psi^{(1)}\left(\beta_\ell^0\right), \tag{25}$$

$$\left(\frac{\partial R_1}{\partial\beta_\ell}\right)_{\boldsymbol{e}^0}=-\psi^{(1)}\left(\beta_\ell^0\right)\left\{\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right\}_{t=\beta_\ell^0}, \tag{26}$$

Recalling the expression of the direct effect term, $\left(\delta R_1\right)^{dir}$, defined in Equation (15), yields the following additional first-order sensitivity:

$$\frac{\partial R_1}{\partial t_d}=-\int_{\beta_\ell^0}^{\beta_u^0}\rho^0(t)\delta'\left(t-t_d^0\right)\mathrm{d}t=\left\{\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right\}_{t=t_d^0} \tag{27}$$

Since neither the direct-effect nor the indirect-effect terms depend on the variation $\partial\beta_u$, it follows that

$$\frac{\partial R_1}{\partial\beta_u}\equiv 0. \tag{28}$$

It is evident from Equations (23) through (27) that the sensitivities of the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$ can be computed by fast quadrature methods applied to the integrals appearing in these expressions, after the 1st-level adjoint function $\psi^{(1)}(t)$ has been obtained by solving *once* the 1st-LASS, which comprises Equations (21) and (22). Notably, the 1st-LASS needs to be solved once only since the 1st-LASS does not depend on any variations in the model parameters or state functions. Particularly important is the response sensitivity to the "initial condition" ρ_{in} since, as Equation (25) indicates, the value of the 1st-level adjoint function $\psi^{(1)}(t)$ at the "initial time-value" $t=\beta_\ell^0$ is proportional to the response sensitivity to the "initial condition". Since the value of the 1st-level adjoint function $\psi^{(1)}(t)$ at $t=\beta_\ell^0$ can be obtained only after computing the entire evolution of $\psi^{(1)}(t)$, from the "final-time" $t=\beta_u^0$ to the "initial-time" $t=\beta_\ell^0$, it becomes apparent that response sensitivities to initial conditions provide a stringent verification procedure for assessing the accuracy of the solution of the 1st-LASS.

Solving the 1st-LASS, cf. Equations (21) and (22), yields the following expression for the 1st-level adjoint function $\psi^{(1)}(t)$:

$$\psi^{(1)}(t)=\left[1-H\left(t-t_d^0\right)\right]\exp\left[\left(t-t_d^0\right)\sum_{i=1}^{N}n_i^0\sigma_i^0\right], \tag{29}$$

where $H(t-t_d)$ is the customary Heaviside unit-step functional, defined as

$$H(t-t_d)\triangleq\begin{cases}1, & t\ge t_d;\\ 0, & t<t_d.\end{cases} \tag{30}$$

Inserting the result from Equation (29) into Equations (23)-(26), respectively, yields the following expressions:

$$\left(\frac{\partial R_1}{\partial\sigma_i}\right)_{e^0}=n_i^0\rho_{in}^0\left(\beta_\ell^0-t_d^0\right)\exp\left[\left(\beta_\ell^0-t_d^0\right)\sum_{i=1}^{N}n_i^0\sigma_i^0\right],\ i=1,\cdots,N, \tag{31}$$

$$\left(\frac{\partial R_1}{\partial n_i}\right)_{e^0}=\sigma_i^0\rho_{in}^0\left(\beta_\ell^0-t_d^0\right)\exp\left[\left(\beta_\ell^0-t_d^0\right)\sum_{i=1}^{N}n_i^0\sigma_i^0\right],\ i=1,\cdots,N, \tag{32}$$

$$\left(\frac{\partial R_1}{\partial\rho_{in}}\right)_{e^0}=\exp\left[\left(\beta_\ell^0-t_d^0\right)\sum_{i=1}^{N}n_i^0\sigma_i^0\right], \tag{33}$$

$$\left(\frac{\partial R_1}{\partial\beta_\ell}\right)_{e^0}=\rho_{in}^0\left(\sum_{i=1}^{N}n_i^0\sigma_i^0\right)\exp\left[\left(\beta_\ell^0-t_d^0\right)\sum_{i=1}^{N}n_i^0\sigma_i^0\right], \tag{34}$$

$$\frac{\partial R_1}{\partial t_d}=-\rho_{in}^0\left(\sum_{i=1}^{N}n_i^0\sigma_i^0\right)\exp\left[\left(\beta_\ell^0-t_d^0\right)\sum_{i=1}^{N}n_i^0\sigma_i^0\right]. \tag{35}$$

The *magnitudes* of the 1st-order *relative sensitivities* provide a quantitative measure for *ranking the importance of the respective parameters in affecting the response* (e.g., the importance of the respective parameter's uncertainty in contributing to the overall uncertainty in the response). For the paradigm illustrative evolution problem considered in this work, Equations (23) and (24) indicate the important fact that the relative sensitivities of the response to the parameters σ_i, $(\partial R_1/\partial\sigma_i)(\sigma_i/R_1)$, and the relative sensitivities of the response to the parameters n_i, $(\partial R_1/\partial n_i)(n_i/R_1)$, respectively, happen to be *identical*, for all of these $2N$ model parameters, since

$$\frac{\partial R_1}{\partial\sigma_i}\frac{\sigma_i}{R_1}=\frac{\sigma_i n_i}{R_1}\int_{\beta_\ell^0}^{\beta_u^0}\left[-\psi^{(1)}(t)\rho(t)\right]\mathrm{d}t\equiv\frac{\partial R_1}{\partial n_i}\frac{n_i}{R_1},\ i=1,\cdots,N. \tag{36}$$

DOI: 10.4236/ajcm.2020.103019

Therefore, statistical methods that use *a priori* screening techniques to *reduce* the number of model parameters that are actually considered in the respective statistical uncertainty/sensitivity analysis will very likely fail to achieve their goal for problems that have many parameters with identical relative sensitivities, as is the case shown in Equation (36). Hence, this illustrative paradigm problem, which has many model parameters that have identical relative sensitivities, would be a prime candidate for testing the various statistical methods for sensitivity and uncertainty analysis. In contrast, a single large-scale computation for obtaining the adjoint function $\psi^{(1)}(t)$ suffices for computing exactly and efficiently, using just quadrature methods, the $2N+4$ sensitivities of the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$ with respect to all model and boundary parameters.

In the particular case when the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$ is located at $t_d=\beta_u$, the expressions of the response sensitivities provided in Equations (31)-(35) remain valid, with the stipulation that $t_d=\beta_u$.

The results for the 1st-order response sensitivities obtained in Section 2.1 can also be verified by noting that the solution of the 1st-LFSS, comprising Equations (16) and (17), has the following expression:

$$\begin{aligned}\delta\rho(t)=&\left\{\rho_{in}^0(\delta\beta_\ell)\sum_{i=1}^{N}n_i^0\sigma_i^0+\delta\rho_{in}+\rho_{in}^0\left(\beta_\ell^0-t\right)\sum_{i=1}^{N}\left(n_i^0\delta\sigma_i+\sigma_i^0\delta n_i\right)\right\}\\&\times\exp\left[\left(\beta_\ell^0-t\right)\sum_{i=1}^{N}n_i^0\sigma_i^0\right],\ 0\le\beta_\ell^0\le t\le\beta_u^0<\infty.\end{aligned}\tag{37}$$

3.2. Computing the 2nd-Order Sensitivities of the Response $R_1(\rho;\alpha,\beta)$ Using Second-Level Adjoint Sensitivity Systems (2nd-LASS)

The starting point for obtaining expressions of the 2nd-order response sensitivities is provided by the G-differentials of the expressions shown in Equations (23)-(27). To keep the notation as simple as possible, the superscript "zero" will henceforth be omitted (except where stringently needed) when denoting "nominal values," since it will be clear from the derivations to follow that all 1st- and 2nd-order sensitivities are to be evaluated at the nominal values of parameters.

3.2.1. Results for the 2nd-Order Response Sensitivities Corresponding to $\partial R_1(\rho;\alpha,\beta)/\partial\sigma_i, i=1,\cdots,N$

The first-order G-differential of Equation (23) yields:

$$\begin{aligned}&\left\{\delta\left(\frac{\partial R_1}{\partial\sigma_i}\right)\right\}_{\boldsymbol{e}^0}\\&\triangleq-\frac{\mathrm{d}}{\mathrm{d}\varepsilon}\left\{(n_i+\varepsilon\delta n_i)\int_{\beta_\ell^0+\varepsilon\delta\beta_\ell}^{\beta_u^0+\varepsilon\delta\beta_u}\left[\psi^{(1)}(t)+\varepsilon\delta\psi^{(1)}(t)\right]\left[\rho(t)+\varepsilon\delta\rho(t)\right]\mathrm{d}t\right\}_{(\boldsymbol{e}=\boldsymbol{e}^0,\varepsilon=0)}\\&=\left\{\left[\delta\left(\frac{\partial R_1}{\partial\sigma_i}\right)\right]_{dir}\right\}_{\boldsymbol{e}^0}+\left\{\left[\delta\left(\frac{\partial R_1}{\partial\sigma_i}\right)\right]_{indir}\right\}_{\boldsymbol{e}^0},\end{aligned}\tag{38}$$

DOI: 10.4236/ajcm.2020.103019

where

$$\text{for } i=1,\cdots,N: \left\{\left[\delta\left(\frac{\partial R_1}{\partial \sigma_i}\right)\right]_{dir}\right\}_{e^0} \triangleq -(\delta n_i)\int_{\beta_\ell^0}^{\beta_u^0}\psi^{(1)}(t)\rho(t)\mathrm{d}t + (\delta\beta_\ell)n_i\psi^{(1)}(\beta_\ell^0)\rho(\beta_\ell^0), \tag{39}$$

$$\text{for } i=1,\cdots,N: \left\{\left[\delta\left(\frac{\partial R_1}{\partial \sigma_i}\right)\right]_{indir}\right\}_{e^0} \triangleq \left\{-n_i\int_{\beta_\ell^0}^{\beta_u^0}\delta\psi^{(1)}(t)\rho(t)\mathrm{d}t - n_i\int_{\beta_\ell^0}^{\beta_u^0}\psi^{(1)}(t)\delta\rho(t)\mathrm{d}t\right\}_{e^0}. \tag{40}$$

The direct-effect term defined by Equation (39) can be computed immediately, since the adjoint function $\psi^{(1)}(t)$ and the forward function $\rho(t)$ are known. However, the indirect-effect term defined by Equation (40) contains the variation $\delta\psi^{(1)}(t)$ in the adjoint function and, respectively, the variation $\delta\rho(t)$ in the forward function, both of which depend on parameter variations and neither of which is immediately available. The variation $\delta\psi^{(1)}(t)$ of the 1st-level adjoint function $\psi^{(1)}(t)$ is related to the parameter variations through the G-differential of the 1st-LASS, which is derived by applying the definition of the G-differential to Equations (21) and (22). Thus, taking the G-differential of the 1st-LASS, cf. Equations (21) and (22), yields the following equations evaluated at the nominal parameter values:

$$-\frac{\mathrm{d}\left[\delta\psi^{(1)}(t)\right]}{\mathrm{d}t} + \delta\psi^{(1)}(t)\sum_{i=1}^{N}n_i\sigma_i = -(\delta t_d)\delta'(t-t_d) - \psi^{(1)}(t)\sum_{i=1}^{N}(n_i\delta\sigma_i + \sigma_i\delta n_i), \quad 0\le\beta_\ell^0\le t\le\beta_u^0<\infty, \tag{41}$$

$$\left\{\delta\psi^{(1)}(t) + (\delta\beta_u)\frac{\mathrm{d}\psi^{(1)}(t)}{\mathrm{d}t}\right\}_{t=\beta_u^0} = \delta\psi^{(1)}(\beta_u^0) = 0. \tag{42}$$

Taken together, Equations (16), (17), (41), and (42) constitute a well-posed system of equations which could, in principle, be solved to obtain the variations $\delta\psi^{(1)}(t)$ and $\delta\rho(t)$ in terms of the parameter variations. However, such a procedure would be just as impractical computationally as solving the 1st-LFSS. Therefore, the need for solving these equations (which depend on parameter variations) will be circumvented by expressing the indirect-effect term defined in Equation (40) in an alternative way so as to eliminate the appearance of $\delta\psi^{(1)}(t)$ and $\delta\rho(t)$. For this purpose, we introduce another Hilbert space, denoted as $\mathsf{H}^{(2)}(\Omega_t), \Omega_t \triangleq (\beta_\ell^0, \beta_u^0)$, which comprises, as elements, two-component vectors of the form $\boldsymbol{\psi}_i^{(2)}(t) \triangleq \left[\psi_{i1}^{(2)}(t), \psi_{i2}^{(2)}(t)\right]$, with square-integrable functions $\psi_{ij}^{(2)}(t), j=1,2$. The inner product between two elements $\boldsymbol{\psi}_i^{(2)}(t) \triangleq \left[\psi_{i1}^{(2)}(t), \psi_{i2}^{(2)}(t)\right] \in \mathsf{H}^{(2)}(\Omega_t)$ and

$\boldsymbol{\varphi}_i^{(2)}(t) \triangleq \left[\varphi_{i1}^{(2)}(t), \varphi_{i2}^{(2)}(t)\right] \in \mathsf{H}^{(2)}(\Omega_t)$ in the Hilbert space $\mathsf{H}^{(2)}(\Omega_t)$ will be denoted as $\left\langle \boldsymbol{\psi}_i^{(2)}(t), \boldsymbol{\varphi}_i^{(2)}(t) \right\rangle_2$ and is defined as follows:

$$\left\langle \boldsymbol{\psi}_i^{(2)}(t), \boldsymbol{\varphi}_i^{(2)}(t) \right\rangle_2 \triangleq \sum_{j=1}^{2} \int_{\beta_\ell^0}^{\beta_u^0} \psi_{ij}^{(2)}(t) \varphi_{ij}^{(2)}(t) \mathrm{d}t. \tag{43}$$

Writing Equations (16) and (41) in matrix form, as follows:

$$\begin{aligned} &\begin{pmatrix} -\dfrac{\mathrm{d}}{\mathrm{d}t} + \sum_{i=1}^{N} n_i \sigma_i & 0 \\ 0 & \dfrac{\mathrm{d}}{\mathrm{d}t} + \sum_{i=1}^{N} n_i \sigma_i \end{pmatrix} \begin{pmatrix} \delta\psi^{(1)}(t) \\ \delta\rho(t) \end{pmatrix} \\ &= \begin{pmatrix} -(\delta t_d)\delta'(t - t_d) - \psi^{(1)}(t) \sum_{i=1}^{N} (n_i \delta\sigma_i + \sigma_i \delta n_i) \\ -\rho(t) \sum_{i=1}^{N} (n_i \delta\sigma_i + \sigma_i \delta n_i) \end{pmatrix}, \end{aligned} \tag{44}$$

and using the definition given in Equation (43), we now construct the inner product of Equation (44) with a square integrable two-component function $\boldsymbol{\psi}_1^{(2)}(t) \triangleq \left[\psi_{11}^{(2)}(t), \psi_{12}^{(2)}(t)\right] \in \mathsf{H}^{(2)}(\Omega_t)$ to obtain the following relation:

$$\begin{aligned} &\int_{\beta_\ell^0}^{\beta_u^0} \left[\psi_{11}^{(2)}(t), \psi_{12}^{(2)}(t)\right] \begin{pmatrix} -\dfrac{\mathrm{d}}{\mathrm{d}t} + \sum_{i=1}^{N} n_i \sigma_i & 0 \\ 0 & \dfrac{\mathrm{d}}{\mathrm{d}t} + \sum_{i=1}^{N} n_i \sigma_i \end{pmatrix} \begin{pmatrix} \delta\psi^{(1)}(t) \\ \delta\rho(t) \end{pmatrix} \mathrm{d}t \\ &= \int_{\beta_\ell^0}^{\beta_u^0} \left[\psi_{11}^{(2)}(t), \psi_{12}^{(2)}(t)\right] \begin{pmatrix} -(\delta t_d)\delta'(t - t_d) - \psi^{(1)}(t) \sum_{i=1}^{N} (n_i \delta\sigma_i + \sigma_i \delta n_i) \\ -\rho(t) \sum_{i=1}^{N} (n_i \delta\sigma_i + \sigma_i \delta n_i) \end{pmatrix} \mathrm{d}t. \end{aligned} \tag{45}$$

Integrating by parts the left-side of Equation (45) so as to transfer the differential operations on $\delta\psi^{(1)}(t)$ and $\delta\rho(t)$ to differential operations on $\psi_{11}^{(2)}(t)$ and $\psi_{12}^{(2)}(t)$ yields the following relation:

$$\begin{aligned} &\int_{\beta_\ell^0}^{\beta_u^0} \psi_{11}^{(2)}(t) \left[-\frac{\mathrm{d}}{\mathrm{d}t} \delta\psi^{(1)}(t) + \delta\psi^{(1)}(t) \sum_{i=1}^{N} n_i \sigma_i \right] \mathrm{d}t \\ &+ \int_{\beta_\ell^0}^{\beta_u^0} \psi_{12}^{(2)}(t) \left[\frac{\mathrm{d}}{\mathrm{d}t} \delta\rho(t) + \delta\rho(t) \sum_{i=1}^{N} n_i \sigma_i \right] \mathrm{d}t \\ &= -\psi_{11}^{(2)}(\beta_u^0) \delta\psi^{(1)}(\beta_u^0) + \psi_{11}^{(2)}(\beta_\ell^0) \delta\psi^{(1)}(\beta_\ell^0) + \psi_{12}^{(2)}(\beta_u^0) \delta\rho(\beta_u^0) \\ &- \psi_{12}^{(2)}(\beta_\ell^0) \delta\rho(\beta_\ell^0) + \int_{\beta_\ell^0}^{\beta_u^0} \delta\psi^{(1)}(t) \left[\frac{\mathrm{d}\psi_{11}^{(2)}(t)}{\mathrm{d}t} + \psi_{11}^{(2)}(t) \sum_{i=1}^{N} n_i \sigma_i \right] \mathrm{d}t \\ &+ \int_{\beta_\ell^0}^{\beta_u^0} \delta\rho(t) \left[-\frac{\mathrm{d}\psi_{12}^{(2)}(t)}{\mathrm{d}t} + \psi_{12}^{(2)}(t) \sum_{i=1}^{N} n_i \sigma_i \right] \mathrm{d}t. \end{aligned} \tag{46}$$

The last two terms on the right-side of Equation (46) will represent the indirect-effect term defined in Equation (40) by requiring that

$$\begin{aligned}&\frac{\mathrm{d}\psi_{11}^{(2)}(t)}{\mathrm{d}t}+\psi_{11}^{(2)}(t)\sum_{i=1}^{N}n_i\sigma_i\\&=-n_i\rho(t)=-n_i\rho_{in}\exp\left[(\beta_\ell-t)\sum_{i=1}^{N}n_i\sigma_i\right],\end{aligned} \tag{47}$$

$$\begin{aligned}&-\frac{\mathrm{d}\psi_{12}^{(2)}(t)}{dt}+\psi_{12}^{(2)}(t)\sum_{i=1}^{N}n_i\sigma_i\\&=-n_i\psi^{(1)}(t)=-n_i\left[1-H(t-t_d)\right]\exp\left[(t-t_d)\sum_{i=1}^{N}n_i\sigma_i\right].\end{aligned} \tag{48}$$

The boundary conditions for Equations (47) and (48) are established by requiring that the contributions involving the unknown quantities $\delta\psi^{(1)}(\beta_\ell^0)$ and $\delta\rho(\beta_u^0)$ in Equation (46) vanish, which can be accomplished by imposing the following conditions:

$$\psi_{11}^{(2)}(\beta_\ell^0)=0,\quad \psi_{12}^{(2)}(\beta_u^0)=0. \tag{49}$$

The system of equations comprising Equations (47)-(49) constitutes the 2nd-Level Adjoint Sensitivity System (2nd-LASS) for the two-component vector-valued function $\boldsymbol{\psi}_1^{(2)}(t)\triangleq\left[\psi_{11}^{(2)}(t),\psi_{12}^{(2)}(t)\right]\in\mathsf{H}^{(2)}(\Omega_t)$, which is called the 2nd-*level adjoint function*. It is important to note that the 2nd-LASS is independent of parameter variations.

Replacing the left-side of Equation (46) by the right-side of Equation (45) and taking into account Equations (47)-(49) yields the following expression for the indirect-effect term defined in Equation (40):

$$\begin{aligned}&\text{for } i=1,\cdots,N:\ \left[\delta\left(\frac{\partial R_1}{\partial\sigma_i}\right)\right]_{indir}\\&=\int_{\beta_\ell^0}^{\beta_u^0}\left[\psi_{11}^{(2)}(t),\psi_{12}^{(2)}(t)\right]\begin{pmatrix}-(\delta t_d)\delta'(t-t_d)-\psi^{(1)}(t)\sum_{i=1}^{N}(n_i\delta\sigma_i+\sigma_i\delta n_i)\\-\rho(t)\sum_{i=1}^{N}(n_i\delta\sigma_i+\sigma_i\delta n_i)\end{pmatrix}\mathrm{d}t\\&+\psi_{11}^{(2)}(\beta_u^0)\delta\psi^{(1)}(\beta_u^0)+\psi_{12}^{(2)}(\beta_\ell^0)\delta\rho(\beta_\ell^0),\end{aligned} \tag{50}$$

Using the conditions given in Equations (17) and (42) in the last terms on the right side of Equation (50) yields the following expression for the indirect-effect term:

$$\begin{aligned}&\text{for } i=1,\cdots,N:\ \left[\delta\left(\frac{\partial R_1}{\partial\sigma_i}\right)\right]_{indir}\\&=\int_{\beta_\ell^0}^{\beta_u^0}\left[\psi_{11}^{(2)}(t),\psi_{12}^{(2)}(t)\right]\begin{pmatrix}-(\delta t_d)\delta'(t-t_d)-\psi^{(1)}(t)\sum_{i=1}^{N}(n_i\delta\sigma_i+\sigma_i\delta n_i)\\-\rho(t)\sum_{i=1}^{N}(n_i\delta\sigma_i+\sigma_i\delta n_i)\end{pmatrix}\mathrm{d}t\\&+\psi_{12}^{(2)}(\beta_\ell)\left\{\delta\rho_{in}-\delta\beta_\ell\left[\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right]_{t=\beta_\ell^0}\right\}.\end{aligned} \tag{51}$$

Adding the direct-effect term defined in Equation (39) to Equation (51) and identifying in the resulting expression the coefficients multiplying the variations $\delta\sigma_i$, δn_i, $\delta\rho_{in}$, δt_d, $\delta\beta_\ell$ and $\delta\beta_u$ yields the following expression for the respective 2nd-order sensitivities of the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$:

$$\frac{\partial^2 R_1}{\partial\sigma_j\partial\sigma_i}=-n_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{11}^{(2)}(t)\psi^{(1)}(t)\mathrm{d}t-n_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{12}^{(2)}(t)\rho(t)\mathrm{d}t;\ i,j=1,\cdots,N; \tag{52}$$

$$\begin{aligned}\frac{\partial^2 R_1}{\partial n_j\partial\sigma_i}=&-\sigma_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{11}^{(2)}(t)\psi^{(1)}(t)\mathrm{d}t-\sigma_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{12}^{(2)}(t)\rho(t)\mathrm{d}t\\&-\delta_{ij}\int_{\beta_\ell^0}^{\beta_u^0}\psi^{(1)}(t)\rho(t)\mathrm{d}t;\quad i,j=1,\cdots,N;\ \delta_{ij}=\begin{cases}1, & i=j;\\0, & i\neq j;\end{cases}\end{aligned} \tag{53}$$

$$\frac{\partial^2 R_1}{\partial\rho_{in}\partial\sigma_i}=\psi_{12}^{(2)}(\beta_\ell);\ \ i=1,\cdots,N; \tag{54}$$

$$\frac{\partial^2 R_1}{\partial t_d\partial\sigma_i}=-\int_{\beta_\ell^0}^{\beta_u^0}\psi_{11}^{(2)}(t)\delta'(t-t_d)=\left[\frac{\mathrm{d}\psi_{11}^{(2)}(t)}{\mathrm{d}t}\right]_{t=t_d};\ \ i=1,\cdots,N; \tag{55}$$

$$\frac{\partial^2 R_1}{\partial\beta_u\partial\sigma_i}=0;\ \ i=1,\cdots,N; \tag{56}$$

$$\frac{\partial^2 R_1}{\partial\beta_\ell\partial\sigma_i}=n_i\psi^{(1)}(\beta_\ell)\rho(\beta_\ell)-\psi_{12}^{(2)}(\beta_\ell)\left[\frac{d\rho(t)}{dt}\right]_{t=\beta_\ell^0};\ \ i=1,\cdots,N. \tag{57}$$

The 2nd-order sensitivities shown in Equations (52)-(57) can be computed after having determined the 2nd-level adjoint function $\boldsymbol{\psi}_1^{(2)}(t)\triangleq\left[\psi_{11}^{(2)}(t),\psi_{12}^{(2)}(t)\right]$ by solving the 2nd-LASS comprising Equations (47)-(49) using the nominal parameter values (the superscript "zero," which indicates "nominal values," has been omitted, for simplicity). Since the model parameters n_i depend on the index $i=1,\cdots,N$, it follows that the right-sides of Equations (47) and (48) also depend on this index. Strictly speaking, therefore, the 2nd-level adjoint sensitivity function $\boldsymbol{\psi}_1^{(2)}(t)\triangleq\left[\psi_{11}^{(2)}(t),\psi_{12}^{(2)}(t)\right]$ is a function of the index $i=1,\cdots,N$. Hence, in the most unfavorable situation, the 2nd-LASS, comprising Equations (47)-(49) would need to be solved numerically for each distinct value n_i, for a total of N-times. Even in such a "worse-case scenario," however, only the right sides (*i.e.*, "sources") of Equations (47) and (48) would need to be modified, which is relatively easy to implement computationally. The left-sides of these equations remain unchanged, since they are independent of the index $i=1,\cdots,N$.

In many practical situations, however, it is possible to reduce drastically the number of computations involving the 2nd-LASS by changing the dependent and/or the independent variables. For example, in the case of the 2nd-LASS comprising Equations (47)-(49), the following simple change of the dependent variables $\psi_{11}^{(2)}(t)$ and $\psi_{12}^{(2)}(t)$:

$$\psi_{11}^{(2)}(t)=n_i\varphi_{11}^{(2)}(t),\ \psi_{12}^{(2)}(t)=n_i\varphi_{12}^{(2)}(t), \tag{58}$$

would transform Equations (47)-(49) into the following form:

$$\frac{d\varphi_{11}^{(2)}(t)}{dt}+\varphi_{11}^{(2)}(t)\sum_{i=1}^{N}n_i\sigma_i=-\rho(t), \tag{59}$$

$$-\frac{d\varphi_{12}^{(2)}(t)}{dt}+\varphi_{12}^{(2)}(t)\sum_{i=1}^{N}n_i\sigma_i=-\psi^{(1)}(t), \tag{60}$$

$$\varphi_{11}^{(2)}(\beta_\ell)=0,\quad \varphi_{12}^{(2)}(\beta_u)=0. \tag{61}$$

The above (alternative) 2nd-LASS, comprising Equations (59)-(61) is *independent* of the index $i=1,\cdots,N$, and *would need to be solved* (numerically or analytically) *only once*, to obtain the following expressions for the functions $\varphi_{11}^{(2)}(t)$ and $\varphi_{12}^{(2)}(t)$:

$$\varphi_{11}^{(2)}(t)=\rho_{in}(\beta_\ell-t)\exp\left[(\beta_\ell-t)\sum_{i=1}^{N}n_i\sigma_i\right], \tag{62}$$

$$\varphi_{12}^{(2)}(t)=(t-t_d)\left[1-H(t-t_d)\right]\exp\left[(t-t_d)\sum_{i=1}^{N}n_i\sigma_i\right]. \tag{63}$$

The components of the 2nd-level adjoint function $\boldsymbol{\psi}_1^{(2)}(t)$ can now be obtained by multiplying the functions $\varphi_{11}^{(2)}(t)$ and $\varphi_{12}^{(2)}(t)$ by the respective model parameters n_i, as indicated in Equation (58), to obtain the following expressions for the components of the 2nd-level adjoint function $\boldsymbol{\psi}_1^{(2)}(t)\triangleq\left[\psi_{11}^{(2)}(t),\psi_{12}^{(2)}(t)\right]$:

$$\psi_{11}^{(2)}(t)=n_i\rho_{in}(\beta_\ell-t)\exp\left[(\beta_\ell-t)\sum_{i=1}^{N}n_i\sigma_i\right], \tag{64}$$

$$\psi_{12}^{(2)}(t)=n_i(t-t_d)\left[1-H(t-t_d)\right]\exp\left[(t-t_d)\sum_{i=1}^{N}n_i\sigma_i\right]. \tag{65}$$

Using Equations (64) and (65) in Equations (52)-(57) and performing the respective operations yields the following results for the respective partial 2nd-order sensitivities:

$$\frac{\partial^2 R_1}{\partial\sigma_j\partial\sigma_i}=\rho_{in}n_jn_i(\beta_\ell-t_d)^2\exp\left[(\beta_\ell-t_d)\sum_{i=1}^{N}n_i\sigma_i\right];\ i,j=1,\cdots,N; \tag{66}$$

$$\begin{aligned}\frac{\partial^2 R_1}{\partial n_j\partial\sigma_i}&=\left[\sigma_jn_i(\beta_\ell-t_d)+\delta_{ij}\right]\rho_{in}(\beta_\ell-t_d)\\&\times\exp\left[(\beta_\ell-t_d)\sum_{i=1}^{N}n_i\sigma_i\right];\ j=1,\cdots,N;\end{aligned} \tag{67}$$

$$\frac{\partial^2 R_1}{\partial\rho_{in}\partial\sigma_i}=n_i(\beta_\ell-t_d)\exp\left[(\beta_\ell-t_d)\sum_{i=1}^{N}n_i\sigma_i\right];\quad i=1,\cdots,N; \tag{68}$$

$$\frac{\partial^2 R_1}{\partial t_d\partial\sigma_i}=-\rho_{in}n_i\left[1+(\beta_\ell-t_d)\sum_{i=1}^{N}n_i\sigma_i\right]\exp\left[(\beta_\ell-t_d)\sum_{i=1}^{N}n_i\sigma_i\right];\ i=1,\cdots,N; \tag{69}$$

$$\frac{\partial^2 R_1}{\partial\beta_u\partial\sigma_i}=0;\quad i=1,\cdots,N; \tag{70}$$

$$\frac{\partial^2 R_1}{\partial\beta_\ell\partial\sigma_i}=\rho_{in}n_i\left[1+(\beta_\ell-t_d)\sum_{i=1}^{N}n_i\sigma_i\right]\exp\left[(\beta_\ell-t_d)\sum_{i=1}^{N}n_i\sigma_i\right];\ i=1,\cdots,N. \tag{71}$$

As before, the right-sides of expressions shown in Equations (66)-(71) are to be evaluated at the nominal values for the parameters, but the superscript "zero," which indicates "nominal values," has been omitted, for notational simplicity.

3.2.2. Results for the 2nd-Order Response Sensitivities Corresponding to $\partial R_1(\rho;\alpha,\beta)/\partial n_i, i=1,\cdots,N$

Computing the first-order G-differential of Equation (24), at the nominal parameter values, yields:

$$\begin{aligned}\left\{\delta\left(\frac{\partial R_1}{\partial n_i}\right)\right\}_{e^0} &\triangleq -\frac{\mathrm{d}}{\mathrm{d}\varepsilon}\left\{(\sigma_i+\varepsilon\delta\sigma_i)\int_{\beta_\ell^0+\varepsilon\delta\beta_\ell}^{\beta_u^0+\varepsilon\delta\beta_u}\left[\psi^{(1)}(t)+\varepsilon\delta\psi^{(1)}(t)\right]\right.\\ &\quad\left.\times\left[\rho(t)+\varepsilon\delta\rho(t)\right]\mathrm{d}t\right\}_{(e=e^0,\varepsilon=0)} \\ &=\left\{\left[\delta\left(\frac{\partial R_1}{\partial n_i}\right)\right]_{dir}\right\}_{e^0}+\left\{\left[\delta\left(\frac{\partial R_1}{\partial n_i}\right)\right]_{indir}\right\}_{e^0},\end{aligned} \tag{72}$$

where the direct-effect and indirect-effect terms, respectively, are evaluated at the nominal parameter values and are defined as follows:

$$\begin{aligned}\left\{\left[\delta\left(\frac{\partial R_1}{\partial n_i}\right)\right]_{dir}\right\}_{e^0} &\triangleq -(\delta\sigma_i)\int_{\beta_\ell^0}^{\beta_u^0}\psi^{(1)}(t)\rho(t)\mathrm{d}t \\ &+(\delta\beta_\ell)\sigma_i\psi^{(1)}(\beta_\ell^0)\rho(\beta_\ell^0),\ \text{for } i=1,\cdots,N;\end{aligned} \tag{73}$$

$$\begin{aligned}\left\{\left[\delta\left(\frac{\partial R_1}{\partial n_i}\right)\right]_{indir}\right\}_{e^0} &\triangleq \left\{-\sigma_i\int_{\beta_\ell^0}^{\beta_u^0}\delta\psi^{(1)}(t)\rho(t)\mathrm{d}t\right\}_{e^0} \\ &-\left\{\sigma_i\int_{\beta_\ell^0}^{\beta_u^0}\psi^{(1)}(t)\delta\rho(t)\mathrm{d}t\right\}_{e^0},\ \text{for } i=1,\cdots,N.\end{aligned} \tag{74}$$

The direct-effect term defined in Equation (73) can be computed immediately, since the adjoint function $\psi^{(1)}(t)$ and the forward function $\rho(t)$ are known. On the other hand, the indirect-effect term defined by Equation (74) contains the variation $\delta\psi^{(1)}(t)$ in the adjoint function and, respectively, the variation $\delta\rho(t)$ in the forward function, both of which depend on parameter variations and neither of which is immediately available. Comparing Equation (74) to Equation (40) readily indicates that the right sides of these equations differ only in that the model parameter σ_i plays in Equation (74) the same role as the model parameter n_i plays in Equation (40). Thus, the same procedure that has been previously used in Section 2.2.1 to obtain an alternative expression for the indirect-effect term defined in Equation (40) by means of a second-level adjoint function is applied to Equation (74) to obtain the following result:

$$\begin{aligned}\text{for } i=1,\cdots,N: \left[\delta\left(\frac{\partial R_1}{\partial n_i}\right)\right]_{indir} &=\psi_{22}^{(2)}(\beta_\ell^0)\left\{\delta\rho_{in}-\delta\beta_\ell\left[\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right]_{t=\beta_\ell^0}\right\}_{e^0} \\ +\int_{\beta_\ell^0}^{\beta_u^0}\left[\psi_{21}^{(2)}(t),\psi_{22}^{(2)}(t)\right]&\begin{pmatrix}-(\delta t_d)\delta'(t-t_d)-\psi^{(1)}(t)\sum_{i=1}^{N}(n_i\delta\sigma_i+\sigma_i\delta n_i)\\ -\rho(t)\sum_{i=1}^{N}(n_i\delta\sigma_i+\sigma_i\delta n_i)\end{pmatrix}_{e^0}\mathrm{d}t.\end{aligned} \tag{75}$$

where the 2nd-level adjoint function $\boldsymbol{\psi}_2^{(2)}(t) \triangleq \left[\psi_{21}^{(2)}(t), \psi_{22}^{(2)}(t)\right]$ satisfies the following 2nd-LASS:

$$\frac{\mathrm{d}\psi_{21}^{(2)}(t)}{\mathrm{d}t} + \psi_{21}^{(2)}(t)\sum_{i=1}^{N} n_i\sigma_i = -\sigma_i\rho_{in}\exp\left[(\beta_\ell - t)\sum_{i=1}^{N} n_i\sigma_i\right], \tag{76}$$

$$-\frac{\mathrm{d}\psi_{22}^{(2)}(t)}{\mathrm{d}t} + \psi_{22}^{(2)}(t)\sum_{i=1}^{N} n_i\sigma_i = -\sigma_i\left[1 - H(t - t_d)\right]\exp\left[(t - t_d)\sum_{i=1}^{N} n_i\sigma_i\right], \tag{77}$$

$$\psi_{21}^{(2)}(\beta_\ell) = 0, \quad \psi_{22}^{(2)}(\beta_u) = 0. \tag{78}$$

The sources on the right-sides of the 2nd-LASS defined by Equations (76)-(78) are to be evaluated at the nominal values for the parameters, but the superscript "zero," which indicates "nominal values," has been omitted, for notational simplicity.

Comparing Equations (76)-(78) to Equations (47)-(49) and recalling Equations (59)-(61) indicates that the components of the 2nd-level adjoint function $\boldsymbol{\psi}_2^{(2)}(t) \triangleq \left[\psi_{21}^{(2)}(t), \psi_{22}^{(2)}(t)\right]$ have the following expressions:

$$\psi_{21}^{(2)}(t) = \sigma_i\varphi_{11}^{(2)}(t) = \sigma_i\rho_{in}(\beta_\ell - t)\exp\left[(\beta_\ell - t)\sum_{i=1}^{N} n_i\sigma_i\right] \tag{79}$$

$$\psi_{22}^{(2)}(t) = \sigma_i\varphi_{12}^{(2)}(t) = \sigma_i(t - t_d)\left[1 - H(t - t_d)\right]\exp\left[(t - t_d)\sum_{i=1}^{N} n_i\sigma_i\right]. \tag{80}$$

Adding the direct-effect term defined in Equation (73) to the expression for the indirect-effect term shown in Equation (75) and identifying in the resulting expression the coefficients multiplying the variations $\delta\sigma_i$, δn_i, $\delta\rho_{in}$, δt_d, $\delta\beta_\ell$ and $\delta\beta_u$ yields the following expression for the respective 2nd-order sensitivities of the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$:

$$\begin{aligned}\frac{\partial^2 R_1}{\partial\sigma_j\partial n_i} &= -n_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{21}^{(2)}(t)\psi^{(1)}(t)\mathrm{d}t - n_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{22}^{(2)}(t)\rho(t)\mathrm{d}t \\ &\quad -\delta_{ij}\int_{\beta_\ell^0}^{\beta_u^0}\psi^{(1)}(t)\rho(t)\mathrm{d}t;\ i,j = 1,\cdots,N;\end{aligned} \tag{81}$$

$$\frac{\partial^2 R_1}{\partial n_j\partial n_i} = -\sigma_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{21}^{(2)}(t)\psi^{(1)}(t)\mathrm{d}t - \sigma_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{22}^{(2)}(t)\rho(t)\mathrm{d}t;\ \ i,j = 1,\ldots,N; \tag{82}$$

$$\frac{\partial^2 R_1}{\partial\rho_{in}\partial n_i} = \psi_{22}^{(2)}(\beta_\ell);\ \ i = 1,\cdots,N; \tag{83}$$

$$\frac{\partial^2 R_1}{\partial t_d\partial n_i} = -\int_{\beta_\ell^0}^{\beta_u^0}\psi_{21}^{(2)}(t)\delta'(t - t_d) = \left[\frac{\mathrm{d}\psi_{21}^{(2)}(t)}{\mathrm{d}t}\right]_{t=t_d};\ \ i = 1,\cdots,N; \tag{84}$$

$$\frac{\partial^2 R_1}{\partial\beta_u\partial n_i} = -n_i\psi^{(1)}(\beta_u)\rho(\beta_u) - \psi_{21}^{(2)}(\beta_u)\left[\frac{\mathrm{d}\psi^{(1)}(t)}{\mathrm{d}t}\right]_{t=\beta_u^0};\ \ i = 1,\cdots,N; \tag{85}$$

$$\frac{\partial^2 R_1}{\partial\beta_\ell\partial n_i} = n_i\psi^{(1)}(\beta_\ell)\rho(\beta_\ell) - \psi_{22}^{(2)}(\beta_\ell)\left[\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right]_{t=\beta_\ell^0};\ \ i = 1,\cdots,N. \tag{86}$$

Inserting the expressions obtained in Equations (79) and (80) for the components of the 2nd-level adjoint function $\boldsymbol{\psi}_2^{(2)}(t) \triangleq \left[\psi_{21}^{(2)}(t), \psi_{22}^{(2)}(t)\right]$ into Equations (81)-(86) yields the following expressions, where all quantities are to be evaluated at the nominal parameter values $\boldsymbol{e}^0 \triangleq \left(\rho^0; \boldsymbol{\alpha}^0, \boldsymbol{\beta}^0\right)$:

$$\begin{aligned} \frac{\partial^2 R_1}{\partial \sigma_j \partial n_i} &= \left[n_j \sigma_i \left(\beta_\ell - t_d\right) + \delta_{ij}\right] \rho_{in} \left(\beta_\ell - t_d\right) \\ &\times \exp\left[\left(\beta_\ell - t_d\right) \sum_{i=1}^{N} n_i \sigma_i\right]; \ j = 1, \cdots, N; \end{aligned} \tag{87}$$

$$\frac{\partial^2 R_1}{\partial n_j \partial n_i} = \rho_{in} \sigma_j \sigma_i \left(\beta_\ell - t_d\right)^2 \exp\left[\left(\beta_\ell - t_d\right) \sum_{i=1}^{N} n_i \sigma_i\right]; \ i, j = 1, \cdots, N; \tag{88}$$

$$\frac{\partial^2 R_1}{\partial \rho_{in} \partial n_i} = \sigma_i \left(\beta_\ell - t_d\right) \exp\left[\left(\beta_\ell - t_d\right) \sum_{i=1}^{N} n_i \sigma_i\right]; \ i = 1, \cdots, N; \tag{89}$$

$$\frac{\partial^2 R_1}{\partial t_d \, \partial n_i} = -\rho_{in} \sigma_i \left[1 + \left(\beta_\ell - t_d\right) \sum_{i=1}^{N} n_i \sigma_i\right] \exp\left[\left(\beta_\ell - t_d\right) \sum_{i=1}^{N} n_i \sigma_i\right]; \ i = 1, \cdots, N; \tag{90}$$

$$\frac{\partial^2 R_1}{\partial \beta_u \partial n_i} = 0; \ i = 1, \cdots, N; \tag{91}$$

$$\frac{\partial^2 R_1}{\partial \beta_\ell \partial n_i} = \rho_{in} \sigma_i \left[1 + \left(\beta_\ell - t_d\right) \sum_{i=1}^{N} n_i \sigma_i\right] \exp\left[\left(\beta_\ell - t_d\right) \sum_{i=1}^{N} n_i \sigma_i\right]; \ i = 1, \cdots, N. \tag{92}$$

3.2.3. Results for the 2nd-Order Response Sensitivities Corresponding to $\partial R_1(\rho; \boldsymbol{\alpha}, \boldsymbol{\beta}) / \partial \rho_{in}$

The 2nd-order response sensitivities corresponding to $\partial R_1(\rho; \boldsymbol{\alpha}, \boldsymbol{\beta}) / \partial \rho_{in}$ will be calculated in this Section by taking the G-differential of Equation (25). Since the model responses need to be written in the form of an inner product in order to apply the adjoint sensitivity analysis methodology, Equation (25) is re-written in the following form:

$$\left(\frac{\partial R_1}{\partial \rho_{in}}\right) = \psi^{(1)}\left(\beta_\ell\right) = \int_{\beta_\ell}^{\beta_u} \psi^{(1)}(t) \delta\left(t - \beta_\ell\right) \mathrm{d}t. \tag{93}$$

Taking the G-differential of Equation (93) yields

$$\begin{aligned} \delta\left(\frac{\partial R_1}{\partial \rho_{in}}\right) &= \frac{\mathrm{d}}{\mathrm{d}\varepsilon} \left\{ \int_{\beta_\ell^0 + \varepsilon \delta \beta_\ell}^{\beta_u^0 + \varepsilon \delta \beta_u} \left[\psi^{(1)}(t) + \varepsilon \delta \psi^{(1)}(t)\right] \delta\left(t - \beta_\ell^0 - \varepsilon \delta \beta_\ell\right) \mathrm{d}t \right\}_{\varepsilon = 0} \\ &= \left\{\delta\left(\frac{\partial R_1}{\partial \rho_{in}}\right)\right\}_{dir} + \left\{\delta\left(\frac{\partial R_1}{\partial \rho_{in}}\right)\right\}_{indir}, \end{aligned} \tag{94}$$

where

$$\left\{\delta\left(\frac{\partial R_1}{\partial \rho_{in}}\right)\right\}_{dir} \triangleq -\left(\delta \beta_\ell\right) \int_{\beta_\ell^0}^{\beta_u^0} \psi^{(1)}(t) \delta'\left(t - \beta_\ell^0\right) \mathrm{d}t, \tag{95}$$

and

$$\left\{\delta\left(\frac{\partial R_1}{\partial \rho_{in}}\right)\right\}_{indir} \triangleq \int_{\beta_\ell^0}^{\beta_u^0} \delta \psi^{(1)}(t) \delta\left(t - \beta_\ell^0\right) \mathrm{d}t. \tag{96}$$

The direct-effect defined in Equation (95) can be computed immediately, since the adjoint function $\psi^{(1)}(t)$ is known. Noteworthy, the indirect-effect term defined in Equation (96) only contains the variation $\delta\psi^{(1)}(t)$ in the 1st-level adjoint function, but does not contain the variation $\delta\rho(t)$ in the forward function, as in Sections 2.2.1 and 2.2.2. Therefore, the 2nd-level adjoint function that would be needed to recast the indirect-effect term defined in Equation (96), by following the same general procedure as used in Sections 2.2.1 and 2.2.2, would be a one-component (as opposed to a "two-component" vector) function. Thus, the 2nd-LASS needed to recast the indirect-effect term defined in Equation (96) is constructed by following a procedure similar to the one that was used in Section 2.1, by applying the definition provided in Equation (18) to construct the inner product of a square-integrable function $\psi_{31}^{(2)}(t) \in \mathsf{H}^{(1)}(\Omega_t)$ with Equation (41) and integrating the left-side of the resulting equation by parts once, so as to transfer the differential operation from $\delta\psi^{(1)}(t)$ onto $\psi_{31}^{(2)}(t)$. This sequence of steps yields the following relation:

$$\begin{aligned}&\int_{\beta_\ell^0}^{\beta_u^0} \psi_{31}^{(2)}(t)\left[-\frac{\mathrm{d}}{\mathrm{d}t}\delta\psi^{(1)}(t)+\delta\psi^{(1)}(t)\sum_{i=1}^{N} n_i\sigma_i\right]\mathrm{d}t \\ &= -\psi_{31}^{(2)}(\beta_u^0)\delta\psi^{(1)}(\beta_u^0)+\psi_{31}^{(2)}(\beta_\ell^0)\delta\psi^{(1)}(\beta_\ell^0) \\ &\quad+\int_{\beta_\ell^0}^{\beta_u^0}\delta\psi^{(1)}(t)\left[\frac{\mathrm{d}\psi_{31}^{(2)}(t)}{\mathrm{d}t}+\psi_{31}^{(2)}(t)\sum_{i=1}^{N} n_i\sigma_i\right]\mathrm{d}t.\end{aligned} \tag{97}$$

The last term on the right-side of Equation (97) is now required to represent the indirect-effect term defined in Equation (96). This is accomplished by requiring that

$$\frac{\mathrm{d}\psi_{31}^{(2)}(t)}{\mathrm{d}t}+\psi_{31}^{(2)}(t)\sum_{i=1}^{N} n_i\sigma_i=\delta(t-\beta_\ell^0), \tag{98}$$

The boundary condition for Equations (98) is established by requiring that the contribution involving the unknown quantity $\delta\psi^{(1)}(\beta_\ell^0)$ in Equation (97) vanish, which can be accomplished by imposing the following condition:

$$\psi_{31}^{(2)}(\beta_\ell^0)=0. \tag{99}$$

As before, Equations (98) and (99), which comprise the 2nd-LASS for the 2nd-level adjoint function $\psi_{31}^{(2)}(t)$, are to be solved at the nominal parameter values.

Replacing the right-side of Equation (41) into the left-side of Equation (97) and taking into account Equations (29), (42) and (99) yields the following expression for the indirect-effect term defined in Equation (96):

$$\left\{\delta\left(\frac{\partial R_1}{\partial\rho_{in}}\right)\right\}_{indir} = -\int_{\beta_\ell^0}^{\beta_u^0}\psi_{31}^{(2)}(t)\left[(\delta t_d)\delta'(t-t_d)+\psi^{(1)}(t)\sum_{i=1}^{N}(n_i\delta\sigma_i+\sigma_i\delta n_i)\right]\mathrm{d}t. \tag{100}$$

Adding the direct-effect term defined in Equation (95) to Equation (100) and identifying in the resulting expression the coefficients multiplying the variations $\delta\sigma_i$, δn_i, $\delta\rho_{in}$, δt_d, $\delta\beta_\ell$ and $\delta\beta_u$ yields the following expressions for the respective 2nd-order sensitivities of the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$:

$$\frac{\partial^2 R_1}{\partial \sigma_j \partial \rho_{in}} = -n_j \int_{\beta_\ell^0}^{\beta_u^0} \psi_{31}^{(2)}(t)\psi^{(1)}(t)\,\mathrm{d}t;\ j=1,\cdots,N; \tag{101}$$

$$\frac{\partial^2 R_1}{\partial n_j \partial \rho_{in}} = -\sigma_j \int_{\beta_\ell^0}^{\beta_u^0} \psi_{31}^{(2)}(t)\psi^{(1)}(t)\,\mathrm{d}t;\ j=1,\cdots,N; \tag{102}$$

$$\frac{\partial^2 R_1}{\partial t_d \partial \rho_{in}} = -\int_{\beta_\ell^0}^{\beta_u^0} \psi_{31}^{(2)}(t)\delta'(t-t_d)\,\mathrm{d}t; \tag{103}$$

$$\frac{\partial^2 R_1}{\partial \rho_{in} \partial \rho_{in}} = 0;\ \frac{\partial^2 R_1}{\partial \beta_u \partial \rho_{in}} = 0; \tag{104}$$

$$\frac{\partial^2 R_1}{\partial \beta_\ell \partial \rho_{in}} = -\int_{\beta_\ell^0}^{\beta_u^0} \psi^{(1)}(t)\delta'(t-\beta_\ell^0)\,\mathrm{d}t = \left\{\frac{\mathrm{d}\psi^{(1)}(t)}{\mathrm{d}t}\right\}_{t=\beta_\ell^0}; \tag{105}$$

The closed-form solution of the 2nd-LASS provided in Equations (98) and (99) has the following expression:

$$\psi_{31}^{(2)}(t) = H(t-\beta_\ell^0)\exp\left[(\beta_\ell^0 - t)\sum_{i=1}^{N} n_i\sigma_i\right], \tag{106}$$

Replacing the result for the 2nd-level adjoint function obtained in Equation (106) into Equations (101)-(103) and carrying out the respective operations yields the following expressions, which are to be evaluated at the nominal parameter values:

$$\frac{\partial^2 R_1}{\partial \sigma_j \partial \rho_{in}} = n_j(\beta_\ell - t_d)\exp\left[(\beta_\ell - t_d)\sum_{i=1}^{N} n_i\sigma_i\right];\ j=1,\cdots,N; \tag{107}$$

$$\frac{\partial^2 R_1}{\partial n_j \partial \rho_{in}} = \sigma_j(\beta_\ell - t_d)\exp\left[(\beta_\ell - t_d)\sum_{i=1}^{N} n_i\sigma_i\right];\ j=1,\cdots,N; \tag{108}$$

$$\frac{\partial^2 R_1}{\partial t_d \partial \rho_{in}} = -\left(\sum_{i=1}^{N} n_i\sigma_i\right)\exp\left[(\beta_\ell - t_d)\sum_{i=1}^{N} n_i\sigma_i\right]; \tag{109}$$

$$\frac{\partial^2 R_1}{\partial \beta_\ell \partial \rho_{in}} = \left(\sum_{i=1}^{N} n_i\sigma_i\right)\exp\left[(\beta_\ell - t_d)\sum_{i=1}^{N} n_i\sigma_i\right]; \tag{110}$$

3.2.4. Results for the 2nd-Order Response Sensitivities Corresponding to $\partial R_1(\rho;\alpha,\beta)/\partial t_d$

The 2nd-order response sensitivities corresponding to $\partial R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})/\partial t_d$ will be calculated in this Section by taking the G-differential of Equation (27), which yields the following expression:

$$\begin{aligned}\delta\left(\frac{\partial R_1}{\partial t_d}\right) &= -\frac{\mathrm{d}}{\mathrm{d}\varepsilon}\left\{\int_{\beta_\ell^0+\varepsilon\delta\beta_\ell}^{\beta_u^0+\varepsilon\delta\beta_u} \left\{\left[\rho^0 + \varepsilon\delta\rho\right]\right\}\delta'(t-t_d^0-\varepsilon\delta t_d)\,\mathrm{d}t\right\}_{\varepsilon=0} \\ &= \left\{\delta\left(\frac{\partial R_1}{\partial t_d}\right)\right\}_{dir} + \left\{\delta\left(\frac{\partial R_1}{\partial t_d}\right)\right\}_{indir},\end{aligned} \tag{111}$$

where

$$\left\{\delta\left(\frac{\partial R_1}{\partial t_d}\right)\right\}_{dir} = -(\delta t_d)\int_{\beta_\ell^0}^{\beta_u^0}\rho(t)\delta''\left(t-t_d^0\right)\mathrm{d}t$$
$$= (\delta t_d)\rho_{in}\left(\sum_{i=1}^{N}n_i\sigma_i\right)^2\exp\left[(\beta_\ell - t_d)\sum_{i=1}^{N}n_i\sigma_i\right], \tag{112}$$

and

$$\left\{\delta\left(\frac{\partial R_1}{\partial t_d}\right)\right\}_{indir} = -\int_{\beta_\ell^0}^{\beta_u^0}\delta\rho(t)\delta'\left(t-t_d^0\right)\mathrm{d}t. \tag{113}$$

Noteworthy, the indirect-effect term defined in Equation (113) only contains the variation $\delta\rho(t)$ in the forward function but does not contain the variation $\delta\psi^{(1)}(t)$ in the 1st-level adjoint function. Therefore, the 2nd-level adjoint function that would be needed to recast the indirect-effect term defined in Equation (113) would be a one-component (as opposed to a two-component vector) function. Thus, the 2nd-LASS needed to recast the indirect-effect term defined in Equation (113) is constructed by following a procedure similar to the one that was used in Section 2.1, by applying the definition provided in Equation (18) to construct the inner product of a square-integrable function $\psi_{41}^{(2)}(t)\in \mathsf{H}^{(1)}(\Omega_t)$ with Equation (16)and integrating the left-side of the resulting equation by parts once, so as to transfer the differential operation from $\delta\rho(t)$ onto the function $\psi_{41}^{(2)}(t)$. This sequence of steps yields the following relation [which is analogous to Equation (19)]:

$$\int_{\beta_\ell^0}^{\beta_u^0}\psi_{41}^{(2)}(t)\left[\frac{\mathrm{d}\left[\delta\rho(t)\right]}{\mathrm{d}t}+\delta\rho(t)\sum_{i=1}^{N}n_i\sigma_i\right]\mathrm{d}t$$
$$= \int_{\beta_\ell^0}^{\beta_u^0}\delta\rho(t)\left[-\frac{\mathrm{d}\psi_{41}^{(2)}(t)}{\mathrm{d}t}+\psi_{41}^{(2)}(t)\sum_{i=1}^{N}n_i\sigma_i\right]\mathrm{d}t \tag{114}$$
$$+\psi_{41}^{(2)}\left(\beta_u^0\right)\delta\rho\left(\beta_u^0\right)-\psi_{41}^{(2)}\left(\beta_\ell^0\right)\delta\rho\left(\beta_\ell^0\right).$$

The following sequence of operations is now performed using Equation (114):

1) Require that the first term on the right-side of Equation (114) be identical with the indirect effect $(\delta R_1)_{indirect}$ defined in Equation (113).

2) Use the right-side of Equation (16) to replace the term multiplying $\psi_{41}^{(2)}(t)$ on the left-side of Equation (114).

3) Eliminate the unknown quantity $\delta\rho\left(\beta_u^0\right)$ on the right-side of Equation (114) by imposing the condition $\psi_{41}^{(2)}\left(\beta_u^0\right)=0$.

4) Insert the boundary condition provided in Equation (17) into Equation (114).

The result of the above sequence of operations is the following expression for the indirect-effect term defined in Equation (113):

$$\left\{\delta\left(\frac{\partial R_1}{\partial t_d}\right)\right\}_{indir} = -\sum_{i=1}^{N}\left(n_i\delta\sigma_i+\sigma_i\delta n_i\right)\int_{\beta_\ell^0}^{\beta_u^0}\psi_{41}^{(2)}(t)\rho(t)\mathrm{d}t$$
$$+\psi_{41}^{(2)}\left(\beta_\ell^0\right)\left[\delta\rho_{in}-\delta\beta_\ell\left\{\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right\}_{t=\beta_\ell^0}\right], \tag{115}$$

where the first-level adjoint function $\psi_{41}^{(2)}(t)$ appearing in Equation (115) is the solution of the following First-Level Adjoint Sensitivity System (1st-LASS) evaluated at the nominal parameter values:

$$-\frac{\mathrm{d}\psi_{41}^{(2)}(t)}{\mathrm{d}t}+\psi_{41}^{(2)}(t)\sum_{i=1}^{N}n_i\sigma_i=-\delta'\left(t-t_d^0\right),\ \ 0\le\beta_\ell^0\le t\le\beta_u^0<\infty, \tag{116}$$

$$\psi_{41}^{(2)}\left(\beta_u^0\right)=0. \tag{117}$$

The solution of Equations (116) and (117) is:

$$\psi_{41}^{(2)}(t)=\delta\left(t-t_d\right)+\left(\sum_{i=1}^{N}n_i\sigma_i\right)\left[H\left(t-t_d\right)-1\right]\exp\left[\left(t-t_d\right)\sum_{i=1}^{N}n_i\sigma_i\right]. \tag{118}$$

In terms of the 2nd-level adjoint function $\psi_{41}^{(2)}(t)$, the partial 2nd-order response sensitivities corresponding to $\partial R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})/\partial t_d$ are obtained by adding Equations (112) and (115), and subsequently identifying in the resulting expression the coefficients multiplying the variations $\delta\sigma_i$, δn_i, $\delta\rho_{in}$, δt_d, $\delta\beta_\ell$ and $\delta\beta_u$. This sequence of operations yields the following expressions:

$$\frac{\partial^2 R_1}{\partial\sigma_j\partial t_d}=-n_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{41}^{(2)}(t)\rho(t)\mathrm{d}t;\ j=1,\cdots,N; \tag{119}$$

$$\frac{\partial^2 R_1}{\partial n_j\partial t_d}=-\sigma_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{41}^{(2)}(t)\rho(t)\mathrm{d}t;\ i,j=1,\cdots,N; \tag{120}$$

$$\frac{\partial^2 R_1}{\partial\rho_{in}\partial t_d}=\psi_{41}^{(2)}\left(\beta_\ell^0\right); \tag{121}$$

$$\frac{\partial^2 R_1}{\partial t_d^2}=\rho_{in}\left(\sum_{i=1}^{N}n_i\sigma_i\right)^2\exp\left[\left(\beta_\ell-t_d\right)\sum_{i=1}^{N}n_i\sigma_i\right]; \tag{122}$$

$$\frac{\partial^2 R_1}{\partial\beta_u\partial t_d}=0; \tag{123}$$

$$\frac{\partial^2 R_1}{\partial\beta_\ell\partial t_d}=-\psi_{41}^{(2)}\left(\beta_\ell^0\right)\left\{\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right\}_{t=\beta_\ell^0}. \tag{124}$$

Replacing the result for the 2nd-level adjoint function obtained in Equation (118) into Equations (119)-(124) and carrying out the respective operations yields the following expressions, which are to be evaluated at the nominal parameter values:

$$\frac{\partial^2 R_1}{\partial\sigma_j\partial t_d}=-n_i\rho_{in}\left[1+\left(\beta_\ell-t_d\right)n_i\sigma_i^2\right]\exp\left[\left(\beta_\ell-t_d\right)\sum_{i=1}^{N}n_i\sigma_i\right];\ j=1,\cdots,N; \tag{125}$$

$$\begin{aligned}\frac{\partial^2 R_1}{\partial n_j\partial t_d}=&-\sigma_i\rho_{in}\left[1+\left(\beta_\ell-t_d\right)\left(\sum_{i=1}^{N}n_i\sigma_i\right)^2\right]\\&\times\exp\left[\left(\beta_\ell-t_d\right)\sum_{i=1}^{N}n_i\sigma_i\right];\ i,j=1,\cdots,N;\end{aligned} \tag{126}$$

$$\frac{\partial^2 R_1}{\partial\rho_{in}\partial t_d}=-\left(\sum_{i=1}^{N}n_i\sigma_i\right)\exp\left[\left(\beta_\ell-t_d\right)\sum_{i=1}^{N}n_i\sigma_i\right]; \tag{127}$$

$$\frac{\partial^2 R_1}{\partial t_d^2} = \rho_{in}\left(\sum_{i=1}^{N} n_i\sigma_i\right)^2 \exp\left[\left(\beta_\ell - t_d\right)\sum_{i=1}^{N} n_i\sigma_i\right]; \tag{128}$$

$$\frac{\partial^2 R_1}{\partial \beta_u \partial t_d} \equiv 0; \tag{129}$$

$$\frac{\partial^2 R_1}{\partial \beta_\ell \partial t_d} = -\rho_{in}\left(\sum_{i=1}^{N} n_i\sigma_i\right)^2 \exp\left[\left(\beta_\ell - t_d\right)\sum_{i=1}^{N} n_i\sigma_i\right]. \tag{130}$$

3.2.5. Results for the 2nd-Order Response Sensitivities Corresponding to $\partial R_1(\rho;\alpha,\beta)/\partial\beta_\ell$

The 2nd-order response sensitivities corresponding to $\partial R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})/\partial t_d$ will be calculated in this Section by taking the G-differential of Equation (26), which first needs to be written in the form of an inner product in order to apply the 2nd-CASAM, as follows:

$$\frac{\partial R_1}{\partial \beta_\ell} = -\left\{\psi^{(1)}(\beta_\ell)\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right\}_{t=\beta_\ell^0} = -\int_{\beta_\ell}^{\beta_u}\left[\psi^{(1)}(t)\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right]\delta(t-\beta_\ell)\mathrm{d}t. \tag{131}$$

Taking the G-differential of Equation (131) at the nominal parameter values (the superscript "zero," denoting nominal values, is again omitted) yields:

$$\begin{aligned}\delta\left(\frac{\partial R_1}{\partial \beta_\ell}\right) &= -\frac{\mathrm{d}}{\mathrm{d}\varepsilon}\left\{\int_{\beta_\ell^0+\varepsilon\delta\beta_\ell}^{\beta_u^0+\varepsilon\delta\beta_u}\left\{\left[\psi^{(1)}+\varepsilon\delta\psi^{(1)}\right]\frac{\mathrm{d}}{\mathrm{d}t}\left[\rho+\varepsilon\delta\rho\right]\right\}\delta\left(t-\beta_\ell^0-\varepsilon\delta\beta_\ell\right)\mathrm{d}t\right\}_{\varepsilon=0} \\ &= \left(\delta\beta_\ell\right)\int_{\beta_\ell^0}^{\beta_u^0}\left[\psi^{(1)}(t)\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right]\delta'\left(t-\beta_\ell^0\right)\mathrm{d}t + \left(\delta\beta_\ell\right)\left[\psi^{(1)}(t)\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right]_{\beta_\ell^0} \\ &\quad -\int_{\beta_\ell^0}^{\beta_u^0}\left[\delta\psi^{(1)}\frac{\mathrm{d}\rho}{\mathrm{d}t}+\psi^{(1)}\frac{\mathrm{d}(\delta\rho)}{\mathrm{d}t}\right]\delta\left(t-\beta_\ell^0\right)\mathrm{d}t.\end{aligned} \tag{132}$$

Using Equations (29) and (8) in the first term on the right-side of Equation (132) yields the following result:

$$\int_{\beta_\ell^0}^{\beta_u^0}\left[\psi^{(1)}(t)\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right]\delta'\left(t-\beta_\ell^0\right)\mathrm{d}t = 0. \tag{133}$$

It is convenient to replace the quantity $\mathrm{d}(\delta\rho)/\mathrm{d}t$, which appears in the last term on the right-side of Equation (132), by using Equation (16) which, together with the result obtained in Equation (133) makes it possible to express the relation in Equation (132) in the following form:

$$\delta\left(\frac{\partial R_1}{\partial \beta_\ell}\right) = \left\{\delta\left(\frac{\partial R_1}{\partial \beta_\ell}\right)\right\}_{dir} + \left\{\delta\left(\frac{\partial R_1}{\partial \beta_\ell}\right)\right\}_{indir}, \tag{134}$$

where

$$\left\{\delta\left(\frac{\partial R_1}{\partial \beta_\ell}\right)\right\}_{dir} = \rho\left(\beta_\ell^0\right)\psi^{(1)}\left(\beta_\ell^0\right)\sum_{i=1}^{N}\left(n_i\delta\sigma_i + \sigma_i\delta n_i\right), \tag{135}$$

and

$$\left\{\delta\left(\frac{\partial R_1}{\partial \beta_\ell}\right)\right\}_{indir} = \int_{\beta_\ell^0}^{\beta_u^0}\left[-\delta\psi^{(1)}(t)\frac{\mathrm{d}\rho(t)}{\mathrm{d}t} + \left(\sum_{i=1}^{N} n_i\sigma_i\right)\psi^{(1)}(t)\delta\rho(t)\right]\delta\left(t-\beta_\ell^0\right)\mathrm{d}t. \quad (136)$$

The indirect-effect term defined in Equation (136) will be expressed in terms of a square integrable two-component adjoint function $\boldsymbol{\psi}_5^{(2)}(t) \triangleq \left[\psi_{51}^{(2)}(t), \psi_{52}^{(2)}(t)\right] \in \mathsf{H}^{(2)}(\Omega_t)$ by first constructing the inner product of Equation (44) with $\boldsymbol{\psi}_5^{(2)}(t)$ to obtain the following relation:

$$\begin{aligned}
&\int_{\beta_\ell^0}^{\beta_u^0}\left[\psi_{51}^{(2)}(t), \psi_{52}^{(2)}(t)\right]\begin{pmatrix} -\frac{\mathrm{d}}{\mathrm{d}t} + \sum_{i=1}^{N} n_i\sigma_i & 0 \\ 0 & \frac{\mathrm{d}}{\mathrm{d}t} + \sum_{i=1}^{N} n_i\sigma_i \end{pmatrix}\begin{pmatrix} \delta\psi^{(1)}(t) \\ \delta\rho(t) \end{pmatrix}\mathrm{d}t \\
&= \int_{\beta_\ell^0}^{\beta_u^0}\left[\psi_{51}^{(2)}(t), \psi_{52}^{(2)}(t)\right]\begin{pmatrix} -(\delta t_d)\delta'(t-t_d) - \psi^{(1)}(t)\sum_{i=1}^{N}(n_i\delta\sigma_i + \sigma_i\delta n_i) \\ -\rho(t)\sum_{i=1}^{N}(n_i\delta\sigma_i + \sigma_i\delta n_i) \end{pmatrix}\mathrm{d}t.
\end{aligned} \quad (1)$$

Integrating by parts the left-side of Equation (137) so as to transfer the differential operations on $\delta\psi^{(1)}(t)$ and $\delta\rho(t)$ to differential operations on $\psi_{51}^{(2)}(t)$ and $\psi_{52}^{(2)}(t)$ yields the following result:

$$\begin{aligned}
&\int_{\beta_\ell^0}^{\beta_u^0}\psi_{51}^{(2)}(t)\left[-\frac{\mathrm{d}}{\mathrm{d}t}\delta\psi^{(1)}(t) + \delta\psi^{(1)}(t)\sum_{i=1}^{N} n_i\sigma_i\right]\mathrm{d}t \\
&+ \int_{\beta_\ell^0}^{\beta_u^0}\psi_{52}^{(2)}(t)\left[\frac{\mathrm{d}}{\mathrm{d}t}\delta\rho(t) + \delta\rho(t)\sum_{i=1}^{N} n_i\sigma_i\right]\mathrm{d}t \\
&= -\psi_{51}^{(2)}\left(\beta_u^0\right)\delta\psi^{(1)}\left(\beta_u^0\right) + \psi_{51}^{(2)}\left(\beta_\ell^0\right)\delta\psi^{(1)}\left(\beta_\ell^0\right) + \psi_{52}^{(2)}\left(\beta_u^0\right)\delta\rho\left(\beta_u^0\right) \\
&- \psi_{52}^{(2)}\left(\beta_\ell^0\right)\delta\rho\left(\beta_\ell^0\right) + \int_{\beta_\ell^0}^{\beta_u^0}\delta\psi^{(1)}(t)\left[\frac{\mathrm{d}\psi_{51}^{(2)}(t)}{\mathrm{d}t} + \psi_{51}^{(2)}(t)\sum_{i=1}^{N} n_i\sigma_i\right]\mathrm{d}t \\
&+ \int_{\beta_\ell^0}^{\beta_u^0}\delta\rho(t)\left[-\frac{\mathrm{d}\psi_{52}^{(2)}(t)}{\mathrm{d}t} + \psi_{52}^{(2)}(t)\sum_{i=1}^{N} n_i\sigma_i\right]\mathrm{d}t.
\end{aligned} \quad (138)$$

The last two terms on the right-side of Equation (138) will represent the indirect-effect term defined in Equation (136) by requiring that

$$\frac{\mathrm{d}\psi_{51}^{(2)}(t)}{\mathrm{d}t} + \psi_{51}^{(2)}(t)\sum_{i=1}^{N} n_i\sigma_i = -\left(\frac{\mathrm{d}\rho}{\mathrm{d}t}\right)\delta\left(t-\beta_\ell^0\right) = \rho_{in}\left(\sum_{i=1}^{N} n_i\sigma_i\right)\delta\left(t-\beta_\ell^0\right), \quad (139)$$

$$\begin{aligned}
&-\frac{\mathrm{d}\psi_{52}^{(2)}(t)}{\mathrm{d}t} + \psi_{52}^{(2)}(t)\sum_{i=1}^{N} n_i\sigma_i = \left(\sum_{i=1}^{N} n_i\sigma_i\right)\psi^{(1)}(t)\delta\left(t-\beta_\ell^0\right) \\
&= \left(\sum_{i=1}^{N} n_i\sigma_i\right)\exp\left[\left(\beta_\ell^0 - t_d^0\right)\sum_{i=1}^{N} n_i\sigma_i\right]\delta\left(t-\beta_\ell^0\right).
\end{aligned} \quad (140)$$

The boundary conditions for Equations (139) and (140) are established by requiring that the contributions involving the unknown quantities $\delta\psi^{(1)}\left(\beta_\ell^0\right)$ and $\delta\rho\left(\beta_u^0\right)$ in Equation (138) vanish, which can be accomplished by imposing the following conditions:

$$\psi_{51}^{(2)}\left(\beta_\ell^0\right)=0,\quad \psi_{52}^{(2)}\left(\beta_u^0\right)=0. \tag{141}$$

Solving Equations (139)-(141) yields the following expressions for the components of the 2nd-level adjoint function $\boldsymbol{\psi}_5^{(2)}(t)\triangleq\left[\psi_{51}^{(2)}(t),\psi_{52}^{(2)}(t)\right]$, to be evaluated at the nominal parameter values:

$$\psi_{51}^{(2)}(t)=\rho_{in}H\left(t-\beta_\ell\right)\left(\sum_{i=1}^{N}n_i\sigma_i\right)\exp\left[\left(\beta_\ell-t\right)\sum_{i=1}^{N}n_i\sigma_i\right], \tag{142}$$

$$\psi_{52}^{(2)}(t)=\left(\sum_{i=1}^{N}n_i\sigma_i\right)\left[1-H\left(t-\beta_\ell^0\right)\right]\exp\left[\left(t-t_d^0\right)\sum_{i=1}^{N}n_i\sigma_i\right], \tag{143}$$

Using Equations (137)-(141) and (17) in Equation (136) yields the following expression for the indirect-effect term defined in Equation (136):

$$\begin{aligned}\left\{\delta\left(\frac{\partial R_1}{\partial\beta_\ell}\right)\right\}_{indir}&=\psi_{52}^{(2)}\left(\beta_\ell\right)\left\{\delta\rho_{in}-\delta\beta_\ell\left[\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right]_{t=\beta_\ell^0}\right\}\\&+\int_{\beta_\ell^0}^{\beta_u^0}\left[\psi_{51}^{(2)}(t),\psi_{52}^{(2)}(t)\right]\begin{pmatrix}-\left(\delta t_d\right)\delta'\left(t-t_d\right)-\psi^{(1)}(t)\sum_{i=1}^{N}\left(n_i\delta\sigma_i+\sigma_i\delta n_i\right)\\-\rho(t)\sum_{i=1}^{N}\left(n_i\delta\sigma_i+\sigma_i\delta n_i\right)\end{pmatrix}\mathrm{d}t\end{aligned} \tag{144}$$

for $i=1,\cdots,N$.

Adding the direct-effect term defined in Equation (135) to Equation (144) and identifying in the resulting expression the coefficients multiplying the variations $\delta\sigma_i$, δn_i, $\delta\rho_{in}$, δt_d, $\delta\beta_\ell$ and $\delta\beta_u$ yields the following expressions for the respective 2nd-order sensitivities of the response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$:

$$\begin{aligned}\frac{\partial^2R_1}{\partial\sigma_j\partial\beta_\ell}&=-n_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{51}^{(2)}(t)\psi^{(1)}(t)\mathrm{d}t-n_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{52}^{(2)}(t)\rho(t)\mathrm{d}t\\&+n_j\rho\left(\beta_\ell^0\right)\psi^{(1)}\left(\beta_\ell^0\right);\ j=1,\cdots,N;\end{aligned} \tag{145}$$

$$\begin{aligned}\frac{\partial^2R_1}{\partial n_j\partial\beta_\ell}&=-\sigma_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{51}^{(2)}(t)\psi^{(1)}(t)\mathrm{d}t-\sigma_j\int_{\beta_\ell^0}^{\beta_u^0}\psi_{52}^{(2)}(t)\rho(t)\mathrm{d}t\\&+\sigma_j\rho\left(\beta_\ell^0\right)\psi^{(1)}\left(\beta_\ell^0\right);\ j=1,\cdots,N;\end{aligned} \tag{146}$$

$$\frac{\partial^2R_1}{\partial\rho_{in}\partial\beta_\ell}=\psi_{52}^{(2)}\left(\beta_\ell\right); \tag{147}$$

$$\frac{\partial^2R_1}{\partial t_d\partial\beta_\ell}=-\int_{\beta_\ell^0}^{\beta_u^0}\psi_{51}^{(2)}(t)\delta'\left(t-t_d\right)=\left[\frac{\mathrm{d}\psi_{51}^{(2)}(t)}{\mathrm{d}t}\right]_{t=t_d}; \tag{148}$$

$$\frac{\partial^2R_1}{\partial\beta_u\partial\beta_\ell}=0; \tag{149}$$

$$\frac{\partial^2R_1}{\partial\beta_\ell\partial\beta_\ell}=-\left[\psi_{51}^{(2)}(t)\frac{\mathrm{d}\rho(t)}{\mathrm{d}t}\right]_{t=\beta_\ell^0}. \tag{150}$$

Inserting the expressions obtained in Equations (142) and (143) for the components of the 2nd-level adjoint function $\boldsymbol{\psi}_5^{(2)}(t)\triangleq\left[\psi_{51}^{(2)}(t),\psi_{52}^{(2)}(t)\right]$ into Equations (145)-(150) yields the following expressions, where all quantities are to be evaluated at the nominal parameter values:

$$\frac{\partial^2 R_1}{\partial \sigma_j \partial \beta_\ell} = n_j \rho_{in} \left[1 + (\beta_\ell - t_d) \sum_{i=1}^{N} n_i \sigma_i \right] \exp\left[(\beta_\ell - t_d) \sum_{i=1}^{N} n_i \sigma_i \right]; \; j = 1, \cdots, N; \quad (151)$$

$$\frac{\partial^2 R_1}{\partial n_j \partial \beta_\ell} = \sigma_j \rho_{in} \left[1 + (\beta_\ell - t_d) \sum_{i=1}^{N} n_i \sigma_i \right] \exp\left[(\beta_\ell - t_d) \sum_{i=1}^{N} n_i \sigma_i \right]; \; j = 1, \cdots, N; \quad (152)$$

$$\frac{\partial^2 R_1}{\partial \rho_{in} \partial \beta_\ell} = \left(\sum_{i=1}^{N} n_i \sigma_i \right) \exp\left[(\beta_\ell - t_d) \sum_{i=1}^{N} n_i \sigma_i \right]; \quad (153)$$

$$\frac{\partial^2 R_1}{\partial t_d \partial \beta_\ell} = -\rho_{in} \left(\sum_{i=1}^{N} n_i \sigma_i \right)^2 \exp\left[(\beta_\ell - t_d) \sum_{i=1}^{N} n_i \sigma_i \right] \quad (154)$$

$$\frac{\partial^2 R_1}{\partial \beta_u \partial \beta_\ell} = 0; \quad (155)$$

$$\frac{\partial^2 R_1}{\partial \beta_\ell \partial \beta_\ell} = \rho_{in} \left(\sum_{i=1}^{N} n_i \sigma_i \right)^2 \exp\left[(\beta_\ell - t_d) \sum_{i=1}^{N} n_i \sigma_i \right]. \quad (156)$$

4. Concluding Remarks

Due to the symmetry of the mixed 2nd-order sensitivities, the following identities hold:

1) The expression provided in Equation (81) must be identical to the expression provided in Equation (53). This identity provides an independent mutual verification of the accuracy of the computations of the 2nd-level adjoint functions $\boldsymbol{\psi}_2^{(2)}(t) \triangleq \left[\psi_{21}^{(2)}(t), \psi_{22}^{(2)}(t) \right]$ and $\boldsymbol{\psi}_1^{(2)}(t) \triangleq \left[\psi_{11}^{(2)}(t), \psi_{12}^{(2)}(t) \right]$.

2) The expression provided in Equation (101) must be identical to the expression provided in Equation (54). This identity provides an independent mutual verification of the accuracy of the computations of the 2nd-level adjoint functions $\boldsymbol{\psi}_3^{(2)}(t) \triangleq \left[\psi_{31}^{(2)}(t), \psi_{32}^{(2)}(t) \right]$ and $\boldsymbol{\psi}_1^{(2)}(t) \triangleq \left[\psi_{11}^{(2)}(t), \psi_{12}^{(2)}(t) \right]$.

3) The expression provided in Equation (102) must be identical to the expression provided in Equation (83). This identity provides an independent mutual verification of the accuracy of the computations of the 2nd-level adjoint functions $\boldsymbol{\psi}_3^{(2)}(t) \triangleq \left[\psi_{31}^{(2)}(t), \psi_{32}^{(2)}(t) \right]$ and $\boldsymbol{\psi}_2^{(2)}(t) \triangleq \left[\psi_{21}^{(2)}(t), \psi_{22}^{(2)}(t) \right]$.

4) The expression provided in Equation (119) must be identical to the expression provided in Equation (55). This identity provides an independent mutual verification of the accuracy of the computations of the 2nd-level adjoint functions $\boldsymbol{\psi}_4^{(2)}(t) \triangleq \left[\psi_{41}^{(2)}(t), \psi_{42}^{(2)}(t) \right]$ and $\boldsymbol{\psi}_1^{(2)}(t) \triangleq \left[\psi_{11}^{(2)}(t), \psi_{12}^{(2)}(t) \right]$.

5) The expression provided in Equation (120) must be identical to the expression provided in Equation (84). This identity provides an independent mutual verification of the accuracy of the computations of the 2nd-level adjoint functions $\boldsymbol{\psi}_4^{(2)}(t) \triangleq \left[\psi_{41}^{(2)}(t), \psi_{42}^{(2)}(t) \right]$ and $\boldsymbol{\psi}_2^{(2)}(t) \triangleq \left[\psi_{21}^{(2)}(t), \psi_{22}^{(2)}(t) \right]$.

6) The expression provided in Equation (121) must be identical to the expression provided in Equation (103). This identity provides an independent mutual verification of the accuracy of the computations of the 2nd-level adjoint functions

$\boldsymbol{\psi}_4^{(2)}(t) \triangleq \left[\psi_{41}^{(2)}(t), \psi_{42}^{(2)}(t)\right]$ and $\boldsymbol{\psi}_3^{(2)}(t) \triangleq \left[\psi_{31}^{(2)}(t), \psi_{32}^{(2)}(t)\right]$.

7) The expression provided in Equation (145) must be identical to the expression provided in Equation (57). This identity provides an independent mutual verification of the accuracy of the computations of the 2nd-level adjoint functions $\boldsymbol{\psi}_5^{(2)}(t) \triangleq \left[\psi_{51}^{(2)}(t), \psi_{52}^{(2)}(t)\right]$ and $\boldsymbol{\psi}_1^{(2)}(t) \triangleq \left[\psi_{11}^{(2)}(t), \psi_{12}^{(2)}(t)\right]$.

8) The expression provided in Equation (146) must be identical to the expression provided in Equation (86). This identity provides an independent mutual verification of the accuracy of the computations of the 2nd-level adjoint functions $\boldsymbol{\psi}_5^{(2)}(t) \triangleq \left[\psi_{51}^{(2)}(t), \psi_{52}^{(2)}(t)\right]$ and $\boldsymbol{\psi}_2^{(2)}(t) \triangleq \left[\psi_{21}^{(2)}(t), \psi_{22}^{(2)}(t)\right]$.

9) The expression provided in Equation (147) must be identical to the expression provided in Equation (105). This identity provides an independent mutual verification of the accuracy of the computations of the 2nd-level adjoint functions $\boldsymbol{\psi}_5^{(2)}(t) \triangleq \left[\psi_{51}^{(2)}(t), \psi_{52}^{(2)}(t)\right]$ and $\psi^{(1)}(t)$.

10) The expression provided in Equation (148) must be identical to the expression provided in Equation (124). This identity provides an independent mutual verification of the accuracy of the computations of the 2nd-level adjoint functions $\boldsymbol{\psi}_5^{(2)}(t) \triangleq \left[\psi_{51}^{(2)}(t), \psi_{52}^{(2)}(t)\right]$ and $\boldsymbol{\psi}_4^{(2)}(t) \triangleq \left[\psi_{41}^{(2)}(t), \psi_{42}^{(2)}(t)\right]$.

The point-detector response $R_1(\rho;\boldsymbol{\alpha},\boldsymbol{\beta})$ considered in this work turned out to be independent of the imprecisely known upper-boundary point β_u, except when the response is located at the nominal value of the uncertain upper boundary (*i.e.*, when the nominal values of the quantities t_d and β_u coincide). In this case, the expressions of the 1st- and 2nd-order response sensitivities derived in this work remain valid, but with the stipulation that t_d is replaced by β_u.

A "reaction-rate" detector response, which depends on both the lower and upper uncertain boundary points, will be considered in the companion work [7] in order to illustrate the possible direct and indirect contributions to the sensitivities of such responses stemming from the uncertain domain boundaries.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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