

# Invalidation of a Heat Shock Model using Sum of Squares Decompositions

## 1 Problem Statement

In this note, we consider model invalidation using experimental measurements and a priori information on the model structure. To maintain consistency, most notation/wording in the first two sections will be borrowed from a recent note by Stephen Prajna [2]. We note that many systems are dependent on some external condition. For example, combustion of methane may depend on the initial pressure. Similarly, the response of E. coli depends on the surrounding temperature (see Section 3.1). We consider systems which are modeled by a set of differential algebraic equations,  $M_c$ :

$$M_c : \dot{x} = f_c(x, y, p) \tag{1}$$

$$0 = g_c(x, y, p) \tag{2}$$

where  $p \in \mathbb{R}^m$  is a parameter vector,  $x \in \mathbb{R}^n$  is a differential state, and  $y \in \mathbb{R}^l$  is an algebraic state.  $c \in \mathbb{R}$  is the 'condition' upon which the model depends.

We assume the parameter vector is known to lie in a set,  $P$ , and the state vector is known to lie in a set,  $X$ :

$$P = \{p \in \mathbb{R}^m : g(p) = 0, h(p) \geq 0\} \tag{3}$$

$$X = \{(x, y) \in \mathbb{R}^n \times \mathbb{R}^l : \bar{g}(x, y) = 0, \bar{h}(x, y) \geq 0\} \tag{4}$$

$M$ ,  $P$ , and  $X$  are the prior information about the system.

Next we assume that experiments are performed at many conditions,  $c_i \in \mathbb{R}$  for  $i = 1, \dots, N$ , and measurements are taken at steady state, i.e. at  $t = \infty$ . Measurements typically come with some uncertainty, so the measurement at condition  $c_i$  is a set:

$$Y_i = \{(x, y) \in \mathbb{R}^n \times \mathbb{R}^l : \tilde{g}_i(x, y) = 0, \tilde{h}_i(x, y) \geq 0\} \tag{5}$$

Given this setup, we can define the model (in)validation problem as follows:

**Problem 1** *Given a priori information  $\{M_c, P, X\}$  and steady state measurements  $\{Y_i\}_{i=1}^N$  observed at conditions  $\{c_i\}_{i=1}^N$ , prove (if possible) that  $\{Y_i\}_{i=1}^N$  is inconsistent with  $\{M_c, P, X\}$ . That is, prove that no parameter,  $p \in P$ , together with the model,  $M_c$ , and state constraints,  $X$ , and conditions  $\{c_i\}_{i=1}^N$ , can produce all measurements in  $\{Y_i\}_{i=1}^N$ .*

## 2 Model Invalidation using Sum of Squares Decompositions

In this section, we present a model invalidation approach that uses sum of squares decompositions. First we note that the model at steady steady is given by:

$$0 = f_c(x, y, p) \tag{6}$$

$$0 = g_c(x, y, p) \tag{7}$$

For a given condition,  $c$ , this model constrains the state and parameter vector to lie in the following set:

$$E_c = \{(x, y, p) \in \mathbb{R}^n \times \mathbb{R}^l \times \mathbb{R}^m : f_c(x, y, p) = 0, g_c(x, y, p) \geq 0\}$$

The set of parameter vectors that are consistent with  $\{M_c, P, X\}$ ,  $\{c_i\}_{i=1}^N$ , and  $\{Y_i\}_{i=1}^N$  is given by:

$$\{p \in P : \exists(x, y) \in X \cap (\cap_{i=1}^N Y_i) \text{ such that } (x, y, p) \in \cap_{i=1}^N E_{c_i}\}$$

If this set is empty, then  $\{Y_i\}_{i=1}^N$  is inconsistent with  $\{M_c, P, X\}$  and  $\{c_i\}_{i=1}^N$ . Equivalently, we can check if the following set is empty:

$$\{(x, y, p) : p \in P, (x, y) \in X \cap (\cap_{i=1}^N Y_i), (x, y, p) \in \cap_{i=1}^N E_{c_i}\}$$

If all the functions involved ( $f$ ,  $g$ , etc.) are polynomial, then we can use sum-of-squares decompositions to prove that this set is empty. We use this approach in the following section. We prove that a model of E. coli heat shock response without a feedforward mechanism is inconsistent with the observations.

## 3 Application to Heat Shock Response of E. coli

### 3.1 Heat Shock Response of E. coli

Kurata, et.al. [1] proposed a biochemical model of the heat shock response in Escherichia coli. The model is a set of differential algebraic equations (DAEs). For simplicity and pedagogical value, we consider a simplified model that has a 4 differential variables and 3 algebraic variables. It has the qualitative features of the full model. The following notation is employed:

$$\begin{aligned} x_1 &:= [mRNA(DnaK)], & x_2 &:= [DnaK]_t, & x_3 &:= [P_{folded}], & x_4 &:= [\sigma^{32}]_t \\ y_1 &:= [\sigma^{32}]_f, & y_2 &:= [DnaK]_f, & y_3 &:= [P_{unfolded}] \end{aligned}$$

All states have units of molecules per cell (these states should take on integer values, a fact that we will ignore in the remainder of the discussion). With these definitions, the heat shock model is given by:

$$\begin{aligned} \dot{x}_1 &= p_5 \cdot y_1 - p_{11} \cdot x_1 \\ \dot{x}_2 &= p_6 \cdot x_1 - p_{12} \cdot x_2 \\ \dot{x}_3 &= (p_9 p_8) \cdot y_3 \cdot y_2 - [(1 - T)p_1 + T p_2] \cdot x_3 \\ \dot{x}_4 &= [(1 - T)p_3 + T p_4] - (p_{10} p_7) \cdot y_1 \cdot y_2 \\ 0 &= y_1 + (p_7 \cdot y_1 \cdot y_2) - x_4 \\ 0 &= y_2 + (p_7 \cdot y_1 \cdot y_2) + (p_8 \cdot y_3 \cdot y_2) - x_2 \\ 0 &= y_3 + x_3 + (p_8 \cdot y_3 \cdot y_2) - p_{13} \end{aligned}$$

where  $p \in \mathbb{R}^{13}$  is the parameter vector and  $T \in [0, 1]$  is the normalized temperature. The parameter values and a further description of this model are given in Appendix A. One key point is that E. coli uses feedforward control in its response to heat stress [1]. As temperature rises, more *DnaK* is required to fold the denatured proteins. The feedforward mechanism in this model is given by the temperature dependence of  $\sigma^{32}$  production ( $\dot{x}_4$ ). Since  $p_4 > p_3$ , the rate of  $\sigma^{32}$  production rises with temperature and this eventually increases  $[DnaK]_t$ .

For the purposes of this example, we will treat this model as the “true” E. coli heat shock response. An “experiment” on E. coli at a given temperature will actually mean a simulation of this truth model.

### 3.2 Model With No Feedforward Mechanism

In this section, we show that sum-of-squares decompositions can be used to invalidate a model that does not include a feedforward mechanism. Thus we can use this algorithm to aid in model construction / validation.

Consider the following heat shock model:

$$\begin{aligned}\dot{x}_1 &= p_5 \cdot y_1 - p_{11} \cdot x_1 \\ \dot{x}_2 &= p_6 \cdot x_1 - p_{12} \cdot x_2 \\ \dot{x}_3 &= (p_9 p_8) \cdot y_3 \cdot y_2 - [(1 - T)p_1 + T p_2] \cdot x_3 \\ \dot{x}_4 &= K_s - (p_{10} p_7) \cdot y_1 \cdot y_2\end{aligned}$$

$$\begin{aligned}0 &= y_1 + (p_7 \cdot y_1 \cdot y_2) - x_4 \\ 0 &= y_2 + (p_7 \cdot y_1 \cdot y_2) + (1e3 \cdot p_8 \cdot y_3 \cdot y_2) - x_2 \\ 0 &= y_3 + x_3 + (p_8 \cdot y_3 \cdot y_2) - p_{13}\end{aligned}$$

$K_s$  is a constant that is assumed to be independent of temperature. In other words, this model of E. coli heat shock response has no feedforward mechanism. This model is of the form given in Equation 1. For this example, we assume that all parameter values are known except  $K_s$ .  $T$  is the temperature (i.e. the condition) at which the experiment is run.

Figure 1 shows the response of this model for  $K_s = 8.1$ . The left subplot shows  $x_4$  (i.e.  $[\sigma^{32}]_t$ ) v.s. time at a low temperature ( $T = 0$ ) while the right subplot is the response at a high temperature ( $T = 1$ ). The shaded areas are the steady state measurements from the “true” heat shock response. For this value of  $K_s$ , the model matches the measurements at low temperatures, but not at high temperatures. Figure 2 shows the model response when  $K_s = 27$ . In this case, the model matches the measurements at high temperatures, but not at low temperatures. We will use sum of squares optimization to prove that this model fails to match both measurements for any  $K_s \in [0.1 \ 10,000]$ .

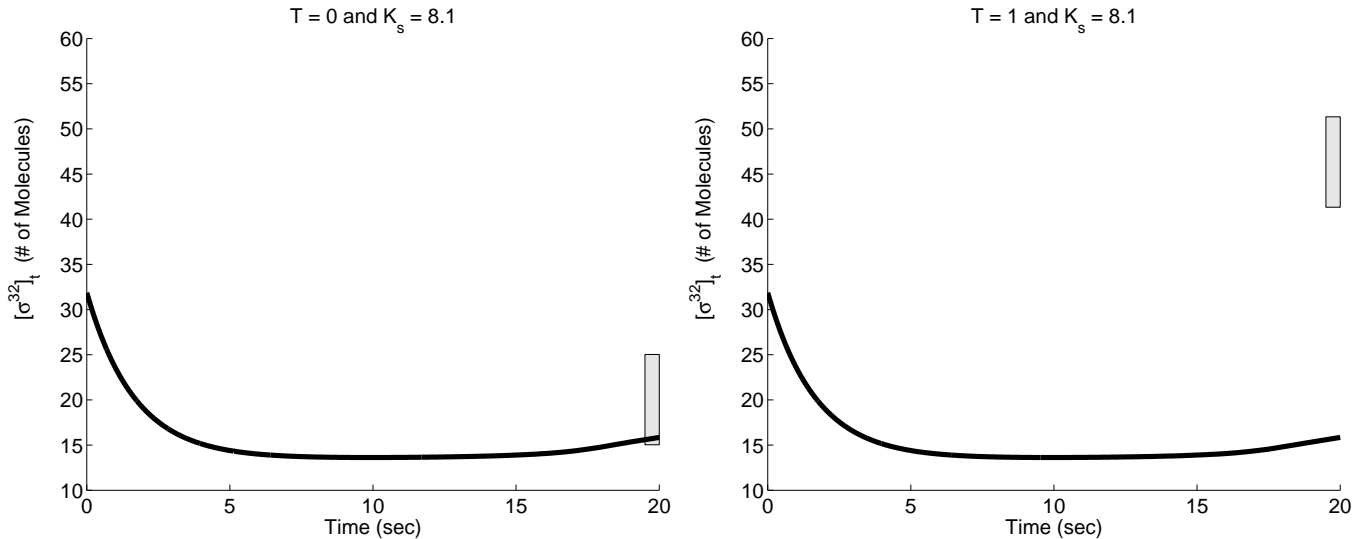


Figure 1:  $x_4$  (i.e.  $[\sigma^{32}]_t$ ) v.s. time for  $K_s = 8.1$  and  $T = 0$  (left subplot) and  $T = 1$  (right subplot). Shaded areas are steady state measurements. Model matches measurements at low temperatures but not at high temperatures.

Next, we define the sets described in Section 1. We assume that the single unknown parameter,  $K_s$ , lies in the interval  $[0.1 \ 10,000]$ . Moreover, we place no constraints on the differential and algebraic states <sup>1</sup>. Thus we have the following constraint sets:

$$P = \{K_s \in \mathbb{R} : K_s \in [0.1 \ 10,000]\} \tag{8}$$

$$X = \mathbb{R}^n \times \mathbb{R}^l \tag{9}$$

At steady state, we can use a symbolic toolbox to eliminate most variables. The steady state model,  $M$ , reduces

<sup>1</sup>We know that these states must be natural numbers since they represent numbers of molecules. We will ignore this additional information

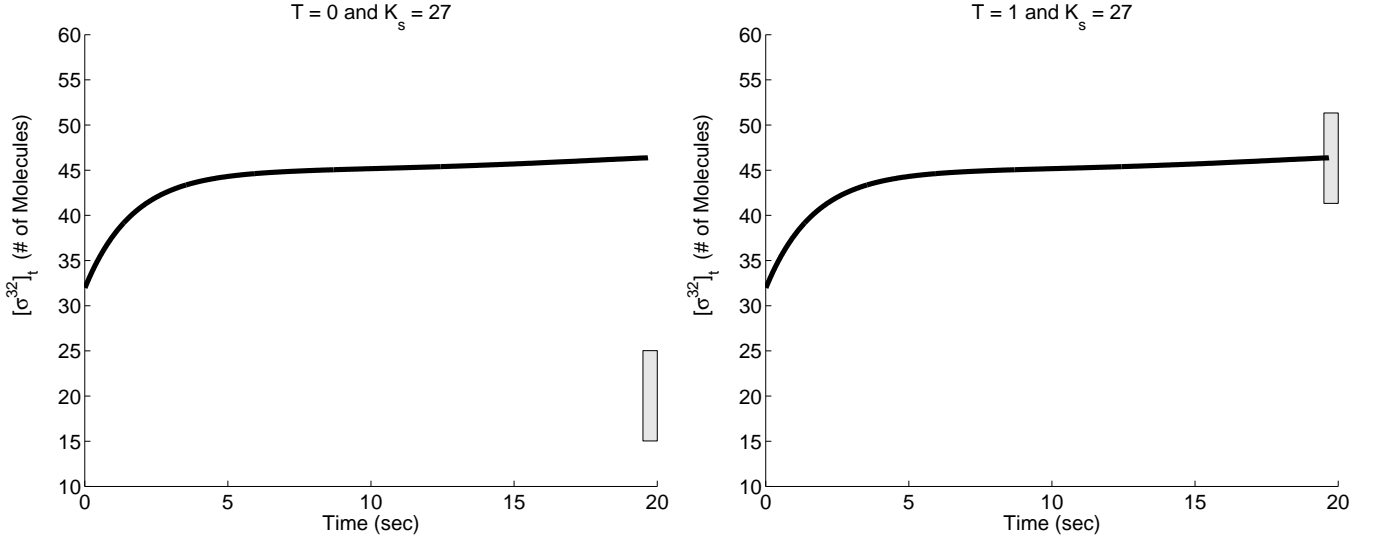


Figure 2:  $x_4$  (i.e.  $[\sigma^{32}]_t$ ) v.s. time for  $K_s = 27$  and  $T = 0$  (left subplot) and  $T = 1$  (right subplot). Shaded areas are steady state measurements. Model matches measurements at high temperatures but not at low temperatures.

to the following set of polynomials:

$$\begin{aligned} c_1(T)y_2^3 + [c_2 + c_3(T)K_s]y_2^2 + c_4(T)K_sy_2 - K_sc_5 &= 0 \\ x_4y_2 - c_6K_s - c_7K_sy_2 &= 0 \end{aligned}$$

where we defined the following constants:

$$\begin{aligned} K_T &:= (1 - T) * p_1 + T * p_2 \\ c_1(T) &:= \frac{p_8(p_9 + K_T)}{K_T} & c_2 &:= 1 + p_8p_{13} \\ c_3(T) &:= \frac{c_1(T)}{p_{10}} & c_4(T) &:= \frac{1}{p_{10}} - c_5c_1(T) \\ c_5 &:= \frac{p_5p_6}{p_7p_{10}p_{11}p_{12}} & c_6 &:= \frac{1}{p_7p_{10}} \\ c_7 &:= \frac{1}{p_{10}} \end{aligned}$$

$M$ ,  $P$ , and  $X$  are the prior information about the system.

We assume that experiments are performed at two conditions,  $T_0 = 0$  and  $T_1 = 1$  (with a slight abuse of notation in the indexing) and the steady state value of  $x_4$  (i.e.  $[\sigma^{32}]_t$ ) is observed with some measurement noise<sup>2</sup>. At  $T = 0$ , we measure  $[\sigma^{32}]_t = 15 \pm 5$  at steady state. At  $T = 1$ , we measure  $[\sigma^{32}]_t = 46 \pm 5$  at steady state. Thus, the measurement sets are described by quadratic constraints:

$$Y_0 = \{(x, z) \in \mathbb{R}^n \times \mathbb{R}^l : (x_4 - 15)^2 \leq 25\} \quad (10)$$

$$Y_1 = \{(x, z) \in \mathbb{R}^n \times \mathbb{R}^l : (x_4 - 46)^2 \leq 25\} \quad (11)$$

We used sum of squares optimization to prove that this set of polynomial constraints is inconsistent. Hence the model without feedforward is inconsistent with the measurements and has been invalidated.

## References

- [1] H. Kurata, H. El-Samad, T.-M. Yi, M. Khammash, and J. Doyle. Feedback regulation of the heat shock response in *E. coli*. In *Proceedings of the 2001 CDC*, 2001.

<sup>2</sup>Recall that this 'observation' is obtained from the 'truth' model described in Section 3.1 with some measurement noise.

[2] Stephen Prajna. Model invalidation—a sum of squares approach. Unpublished, September 2002.

## A Heat Shock Model Notation

In this section, we describe the notation used in the heat shock model. The following notation is employed:

$$\begin{aligned}
[X]_t &= \text{Total quantity of species X (molecules/cell)} \\
[X]_f &= \text{Free quantity of species X (molecules/cell)} \\
[X : Y] &= \text{Complex formed by the binding of X and Y (molecules/cell)} \\
mRNA(X) &= \text{Messenger RNA that encodes for protein X}
\end{aligned}$$

The model is given by:

$$\begin{aligned}
\frac{d}{dt}[mRNA(DnaK)] &= K_{tr}[\sigma^{32}]_f - \alpha_m[mRNA(DnaK)] \\
\frac{d}{dt}[DnaK]_t &= K_{tl}[mRNA(DnaK)] - \alpha_d[DnaK]_t \\
\frac{d}{dt}[P_{folded}] &= K_f[P_{unfolded} : DnaK] - K_T[P_{folded}] \\
\frac{d}{dt}[\sigma^{32}]_t &= K_s - K[\sigma^{32} : DnaK]
\end{aligned}$$

$$\begin{aligned}
[\sigma^{32} : DnaK] &= K_1[\sigma^{32}]_f \cdot [DnaK]_f \\
[P_{unfolded} : DnaK] &= K_2[P_{unfolded}] \cdot [DnaK]_f \\
[\sigma^{32}]_t &= [\sigma^{32}]_f + [\sigma^{32} : DnaK] \\
[DnaK]_t &= [DnaK]_f + [\sigma^{32} : DnaK] + [P_{unfolded} : DnaK] \\
[P]_t &= [P_{unfolded}] + [P_{folded}] + [P_{unfolded} : DnaK]
\end{aligned}$$

$[P]_t$  is assumed to be a constant and two parameters are assumed to be temperature dependent:

$$\begin{aligned}
K_T &= (1 - T) \cdot p_1 + T \cdot p_2 \\
K_s &= (1 - T) \cdot p_3 + T \cdot p_4
\end{aligned}$$

where  $\{p_i\}_{i=0}^4$  are new constants and  $T \in [0, 1]$  is the normalized temperature. The actual temperature is  $T_{actual} = (1 - T) \cdot 36^\circ C + T \cdot 42^\circ C$ .

As noted in Kurata, et.al. [1], E. coli uses both feedback and feedforward control in its response to heat stress. Briefly, the feedforward mechanism is given by the temperature dependence of  $K_s$ . Consequently, the rate of  $\sigma^{32}$  production rises with temperature and this eventually increases  $[DnaK]_t$ . The feedback mechanism is given by the term  $-K[\sigma^{32} : DnaK]$  in the fourth differential equation. Large values of  $[\sigma^{32} : DnaK]$  imply excessive amounts of  $[DnaK]_t$ . The term  $-K[\sigma^{32} : DnaK]$  slows the rate of  $\sigma^{32}$  production when  $[\sigma^{32} : DnaK]$  is large.

To simplify the model, we eliminate two of the algebraic constraints. Specifically, we eliminate  $[P_{unfolded} : DnaK]$  and  $[\sigma^{32} : DnaK]$ . We define the states, algebraic variables, and fixed parameters as:

$$\begin{aligned}
x_1 &:= [mRNA(DnaK)], & x_2 &:= [DnaK]_t, & x_3 &:= [P_{folded}], & x_4 &:= [\sigma^{32}]_t \\
y_1 &:= [\sigma^{32}]_f, & y_2 &:= [DnaK]_f, & y_3 &:= [P_{unfolded}] \\
p_5 &:= K_{tr}, & p_6 &:= K_{tl}, & p_7 &:= K_1, & p_8 &:= K_2, \\
p_9 &:= K_f, & p_{10} &:= K, & p_{11} &:= \alpha_m, & p_{12} &:= \alpha_d, \\
p_{13} &:= [P]_t
\end{aligned}$$

With these definitions, the heat shock model is given by:

$$\begin{aligned}\dot{x}_1 &= p_5 \cdot y_1 - p_{11} \cdot x_1 \\ \dot{x}_2 &= p_6 \cdot x_1 - p_{12} \cdot x_2 \\ \dot{x}_3 &= (p_9 p_8) \cdot y_3 \cdot y_2 - [(1 - T)p_1 + T p_2] \cdot x_3 \\ \dot{x}_4 &= [(1 - T)p_3 + T p_4] - (p_{10} p_7) \cdot y_1 \cdot y_2\end{aligned}$$

$$\begin{aligned}0 &= y_1 + (p_7 \cdot y_1 \cdot y_2) - x_4 \\ 0 &= y_2 + (p_7 \cdot y_1 \cdot y_2) + (p_8 \cdot y_3 \cdot y_2) - x_2 \\ 0 &= y_3 + x_3 + (p_8 \cdot y_3 \cdot y_2) - p_{13}\end{aligned}$$

We assume the parameter values are given by:

$$\begin{array}{llll} p_1 = 75, & p_2 = 150 & p_3 = 8.1, & p_4 = 27 \\ p_5 = 3.75, & p_6 = 20.0 & p_7 = 2.54e - 2, & p_8 = 2.54e - 3 \\ p_9 = 1.5e4, & p_{10} = 0.6 & p_{11} = 0.5, & p_{12} = 3.0e - 2 \\ p_{13} := 2e6 & & & \end{array}$$