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Screening Parameters of Pulmonary and Cardiovascular Integrated Model with Sensitivity Analysis

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***Abstract*— Previously, we built a pulmonary and cardiovascular integrated model which is driven by O2 consumption. However this model is adjusted to average person and cannot correspond to individual difference. It needs parameter adjustment to be applied for simulation of a particular person. We used *lumped parameter models*, which have simple structures and are well suited to macro-model. However they have a drawback that the number of parameters becomes large if the model describes organs in detail. Since our model has more than 100 parameters, it is ineffective to estimate all parameters. For efficient parameter tuning, we selected important parameters which have significant influence on outputs with a kind of sensitivity analysis method. The model can be well approximated only by the important parameters.**

I. Introduction

Recently, there is growing concern about everyday healthcare. In monitoring the health of human in daily life, the number of sensors should be preferably small not to constrain human body. However, limited kinds of vital signs are measured directly with a few sensors. Therefore, it is helpful to complement the limited amount of vital signs with prediction by human models.

Previously, we built a pulmonary and cardiovascular integrated model that expresses adjustments of respiration and circulation according to O2 consumption [1]. However the model is adjusted to an average person, it cannot correspond to individual difference.

Parameter estimation is necessary to apply the model to individuals, but it is not realistic to adjust all parameters because our model contains more than 100 parameters. When we settle a variable in the model for the output, we have to decide which parameters are adjusted especially in precise. We selected important parameters which have large influence on the model's output by means of a sensitivity analysis method.

II. The Integrated Model

A. Overall Structure of the Integrated Model

The integrated model is composed of two controller models and three organ mechanical models. The controllers are cardiovascular [2] and respiratory [3] control models. The mechanical models are cardiovascular [2], airway·lung [4] and gas exchange [5] models. These models are interacting with one another as shown in Fig. 1.

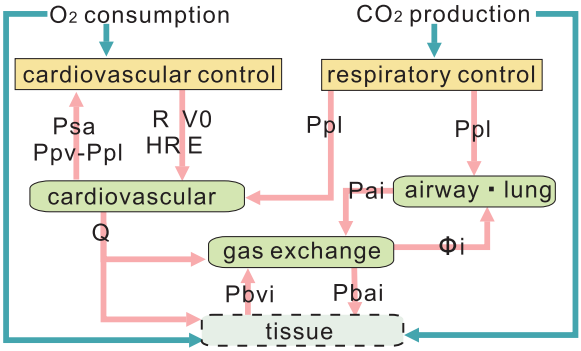

Fig. 1. Overall structure of the integrated model. Ppl: pleural pressure, Psa: arterial pressure, Ppv: pressure in pulmonary vein, R/V0: resistance/zero pressure volume of blood vessel, HR: heart-rate, E: ventricular elastance, i: gas species (O_2 and CO_2) Q: blood flow rate, Pai: partial pressure of gas i in alveolar region, Φ_i: transfer rate of gas i between blood and alveolar region, Pbvi: partial pressure of gas i in venous blood, Pbai: partial pressure of gas i in arterial blood

The overall inputs are O_2 consumption and CO_2 production. The cardiovascular control model adjusts parameters of the cardiovascular model such as blood vessel resistances, zero pressure volumes, heart-rate and ventricular elastance according to arterial pressure, pressure in pulmonary vein and O_2 consumption. The cardiovascular model is driven by time-varying ventricular elastance. The respiratory control model calculates pleural pressure from the CO_2 production. The airway·lung model is driven by the pleural pressure. In the cardiovascular model, blood vessels in the thorax are influenced by the pleural pressure. The gas exchange model receives blood flow rate in pulmonary capillary from the cardiovascular model, and O_2 and CO_2 partial pressures in alveolar region from the airway·lung model. The gas exchange model returns O_2 and CO_2 transfer rates between blood and the alveolar region to the airway·lung model. The boundary condition of the gas exchange model is O_2 and CO_2 partial pressures in venous blood. They are determined by O_2 and CO_2 partial pressures in arterial blood, the O_2 consumption, the CO_2 production and blood flow rate. This is described as "tissue" in Fig. 1. The respiratory exchange rate is assumed to be constant, hence the CO_2 production is determined by the O_2 consumption.

B. Lumped Parameter Model and the Number of Parameters

The Cardiovascular model and the airway-lung model are both lumped parameter models. Lumped parameter models are described mathematically by a set of first order ordinary differential equations. Therefore, the lumped parameter models have simple structures and are well suited to macro-model. However it has a drawback that the number of parameters become large if the model describes organs in detail. Table I shows the number of parameters. The integrated model has more than 100 parameters. Therefore, they cannot be estimated all at once.

III. Screening Parameters

We selected important parameters by the following sensitivity analysis exercise. Sensitivity analysis is the study of how variation in the output of model can be apportioned, qualitatively or quantitatively, to different source of variation [7].

A. The Method of Morris

We used the method of Morris [6][7] for screening parameters. The guiding philosophy of the Morris method is to determine which factors may be considered to have effects which are (a) negligible, (b) linear and additive, or (c) non-linear or involved in interactions with other factors.

Assume that the k-dimensional vector $\mathbf{X}$ of the model input has components X_i each of which can assume integer values in the set $\{0, 1/(p-1), 2/(p-1), \cdots, 1\}$. The region of experimentation, Ω, will then be a *k*-dimensional *p*-level grid. In practical applications, the values sampled in Ω are subsequently rescaled to generate the actual values assumed by the input factors.

The Morris method is based on what is called an *elementary effect*. The elementary effect for the *i* th input is defined as follows. Let Δ be a predetermined multiple of $1/(p-1)$. For a given value $\mathbf{x}$ of $\mathbf{X}$, the elementary effect of the *i* th input factor is defined as

$$d_i(\mathbf{x}) = \frac{y(\mathbf{x} + \mathbf{e}_i\Delta) - y(\mathbf{x})}{\Delta}, \tag{1}$$

where y is model's output, where $\mathbf{x} = (x_1, x_2, \cdots, x_k)$ is any selected value in Ω such that the transformed point $(\mathbf{x} + \mathbf{e}_i\Delta)$, where $\mathbf{e}_i$ is a vector of zeros but with a unit as its *i* th component, is still in Ω for each index $i = 1, \cdots, k$.

The sensitivity measures are μ^*, the mean of the absolute values of the elementary effects and σ, the standard deviation of the elementary effects. μ^* is used to detect input factors with an important overall influence on the output. σ is used to detect factors involved in interaction with other factors or whose effect is non-linear.

TABLE I

THE NUMBERS OF PARAMETERS

model	the number of parameters
cardiovascular	57
cardiovascular control	58
airway-lung	28
respiratory control	11
gas exchange	6

B. Apply the Method to the Model

There are two main problems in applying the method of Morris to our pulmonary and cardiovascular integrated model.

1) distribution assumption of parameters
2) numerical integration for outputs

1) the distribution of the parameters: We have to decide the upper bounds, the lower bounds, and the shape of the distribution of the parameters in applying the method of Morris to the model. However it is difficult to physiologically explain all the distributions of the parameters more than 100. Therefore, we focus on checking not physiological but numerical properties of the model at first.

We assume the values reported in literature as median of parameters, and set their upper bounds and lower bounds $\pm 20\%$ from them. For the shape of distribution, we adopt middle 90 percent of normal distribution (Fig. 2).

There are of course problems in deciding automatically the bounds and the shapes of distributions of parameters. For instance, parameters which have nonlinear effects on outputs show different sensitivities according to different bounds. Another problem is that when one parameter and another have a certain relationship, e.g., one means upper and the other means lower bound of some physiologic amount, random sampling might violate the relationship. This causes failure of simulation.

The distributions of the parameters selected by the screening method should be examined physiologically. We manually corrected obviously wrong distributions and applied the screening method again.

2) numerical integration: Since the model is described by ordinary differential equations, we have to solve them numerically to obtain outputs. This causes following two problems. The time consuming calculation is one. The other is that simulation becomes unstable and often fails with certain parameter sets.

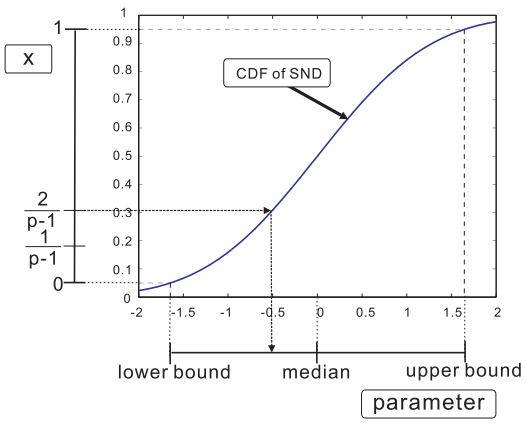

Fig. 2. How to sample the value of the parameter from normalized 'x'. The curve is cumulative distribution function of standard normal distribution. The figure shows an example of sampling parameter value when x equals $2/(p-1)$.

To solve the first problem, the model was divided. The larger and the more complex the model is, the smaller the time step size tends to be. Consequently, simulation costs more time.

Next, we detected the parameters which contribute to the instability of the simulation and modified the bounds of such parameters not to drive simulation failure.

3) Dividing the Model: Here, we call the components of the integrated model "sub models". Inputs to sub models are classified following three kinds of factors.

1) initial conditions
2) parameters
3) inputs from other sub models

The first and second are constant while one simulation, but the third is time-varying. The screening method cannot deal with time-varying factors. However the third factors are described by parameters of the sub models which output them.

For example, assume that four sub models are integrated as Fig. 3. When the numbers of parameters of model1, 2, 3 and 4 are $n1$, $n2$, $n3$ and $n4$, that of the integrated model is $n1 + n2 + n3 + n4$. The variable, $output1$, is described by time and $n1$ parameters but after screening $n1$ parameters, it can be approximated by $m1$ ($< n1$) important parameters. The variable $output2$ is described by $m1+n2$ parameters, but is approximated by $m2$ ($< m1 + n2$) important parameters. $output3$ is approximated by $m3$ ($< n4$) parameters and $output4$ (the output of the integrated model) is by $m4$ ($< m2 + m3 < n1 + n2 + n3 + n4$) parameters by the same token. Thus the number of the factors screened at one time is reduced by dividing the model into sub models.

However, this method of division does not work for the part which contains feedback loop. Such part of the model have to be unified and dealt as one model. In the integrated model, there is a feedback loop between cardiovascular and its control model.

4) Avoiding Failure of Simulation: There is unstable region in the space of the input factors whose boundary is automatically decided. In this boundary the simulation sometimes fails. For example, we pick up cardiovascular model which has 71 input factors. When we sampled 5,000 points at random from 71-dimensional hyper-cube and simulated 5,000 times, 378 simulations failed. If we find the part in which simulation fails from the input factor space in advance, we need not to examine sensitivity in that part.

We used regionalized sensitivity analysis (RSA) [7] to find which factors render the simulation unstable and to modify their bounds. The sensitivity measure of RSA examined about every input factors. The measure $d_{m,n}$ is defined by

$$d_{m,n} = \sup \|F_m - F_n\|, \tag{2}$$

where F_m is the marginal cumulative probability function of samples in which simulation succeeds, and F_n is that of samples in which simulation fails. If $d_{m,n}$ is large, the distribution varies widely according to whether simulation succeeds or fails. The factors which have large $d_{m,n}$ consequently contribute to failure of simulation.

We calculated all the RSA measures of the cardiovascular model and sorted them (Fig.4). The 17th and the 50th input factors seem to make simulation fail. Since the samples in which simulation fails of the 17th and the 50th factors are distributed near lower bound and upper bound each, we shift the median of the 17th by 150% and that of the 50th by 70%. In consequence, the samples in which simulation fails were reduced from 378/5000 to 23/5000.

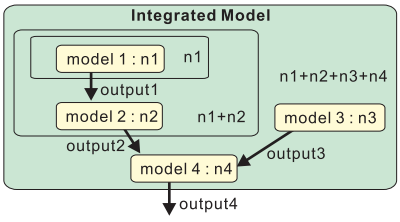

Fig. 3. Example of division of model. n1, n2, n3, n4 are the numbers of parameters of each sub model.

IV. RESULT

The results of sensitivity analysis for each sub model are shown following figures (Fig. 5, 6, 7, 8). The horizontal axis is μ^*, the mean of the absolute values of the elementary effects, (eq.1), and the vertical axis is σ, the standard deviation of the elementary effects.

We use the dividing method described in section III in screening the parameters of the cardiovascular, airway-lung and gas exchange integrated model (Fig. 8).

V. VALIDATION

We verified the validity of the screening method on the models in the following way. Assume that the model structure is correct and only parameter adjustments are needed for fitting the model to individual. Under this assumption, we sample two random parameter sets and take one as a *human organ* and the other as a *model*. We define the error as following equation,

$$error = \int_{t1}^{t2} |y_h - y_m| dt/(t2 - t1), \tag{3}$$

where y_h is the output of the *human organ*, and y_m is that of the *model*. Then replace, one-by-one, the parameters of the *model* to those of the *human organ* in order of sensitivity measure μ^*, and in random order. Fig. 9 and Fig. 10 show that the error decreases faster when the parameters are replaced in the order of sensitivity measure.

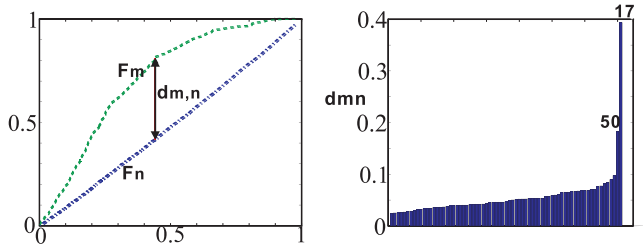

Fig. 4. The left figure shows the definition of the sensitivity measure $d_{m,n}$. F_m is the marginal cumulative probability function of samples in which simulation succeeds and F_n is that of samples in which simulation fails. The right figure is sorted $d_{m,n}$s of every cardiovascular input factors

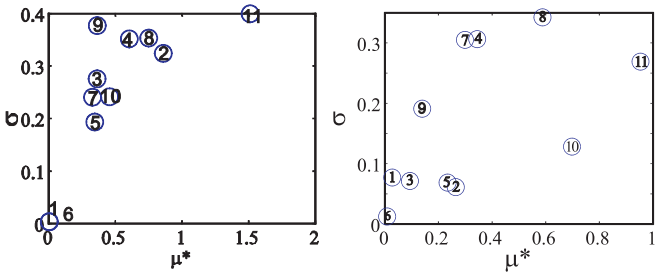

Fig. 5. The results of the Morris experiments on the respiratory control model. The outputs are the period (left) and the amplitude (right) of the pleural pressure. The important factors are (left) 11: weighting factor of mechanical cost of inspiration, 2: metabolic CO_2 output, 8: the compliance of the lung, 4: chemoreceptor response threshold, (right) 11, 10: vital capacity, 8, 4, 7: total respiratory system resistance.

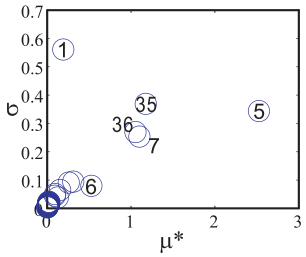

Fig. 6. The result of the Morris experiment on the airway-lung model. The output is tidal volume. Only the important factors are labeled. 5: alveolar volume at end inspiration. 35: inspiration duration. 7: the maximum lung elastic recoil. 36: expiration duration. The nonlinear factor, 1: initial volume of lung.

VI. CONCLUSION

We detected important parameters of the pulmonary and cardiovascular integrated model by applying the screening method to the model. Validity of the screening was examined by comparing the errors of the model whose important parameters were adjusted and that of the model whose randomly selected parameters were adjusted.

VII. ACKNOWLEDGMENT

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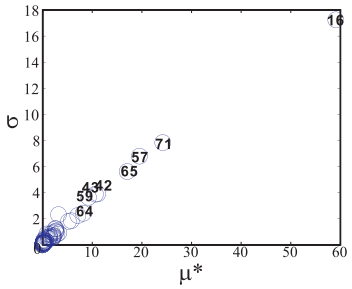

Fig. 7. The result of the Morris experiment on the cardiovascular model. The output is cardiac output. The important input factors are 16: total amount of blood contained in cardiovascular system, 71: heart period, 57 and 65: constant parameter that characterize the monoexponential pressure/volume function of left and right ventricle, 42 and 43: splanchnic and extrasplanchnic venous unstressed volume.

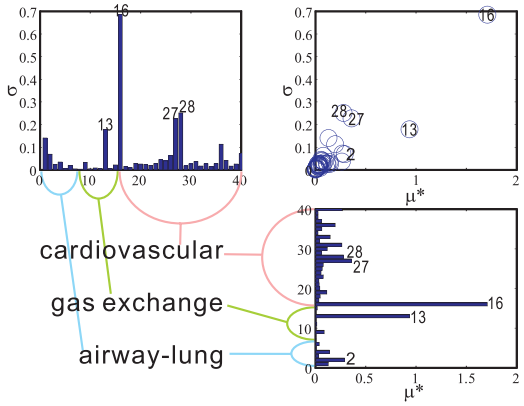

Fig. 8. The result of the Morris experiment on the gas exchange model. The important parameters of the cardiovascular model and the airway-lung model were screened in addition to the gas exchange parameters. The output is rate of transfer of O_2 between blood and alveolar region. The important factors are 16: total amount of blood contained in cardiovascular system, 13: initial condition of O_2 partial pressure in alveolar region, 27 and 28: splanchnic and extrasplanchnic venous unstressed volume. 2: alveolar volume at end inspiration.

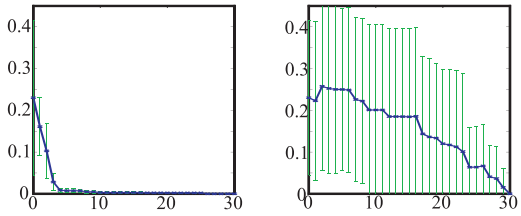

Fig. 9. Validation of the screening method on the airway-lung model. The horizontal axis is the number of the replaced parameters. The vertical axis is the error. The line is the mean value of the error and error bars of 10 trials. The error decreases faster when the parameters are replaced in the order of the sensitivity measure (left) than when in random order (right).

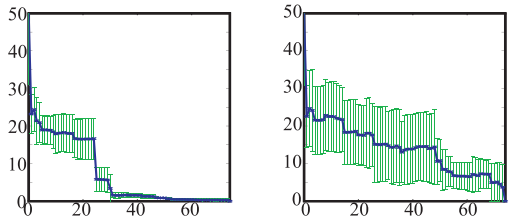

Fig. 10. Validation of the screening method on the cardiovascular model. The error decreases faster when the parameters are replaced in the order of the sensitivity measure (left) than when in random order (right).