Report on a problem studied at the UK Mathematics-in-Medicine Study Group Southampton 2007
< https://mmsg.mathmos.net/uk/2007/decompression-sickness/ >

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Parameter estimation in decompression sickness

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Summary Presentation given by S Waters and J Forster (14 Sept 2007)
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1 Introduction

It is critical that scuba divers and submariners can assess the possible effects of changes in pressure of their surrounding atmosphere as otherwise they may be affected by the "bends" (or, to use its more formal name, Decompression Sickness (DCS)) which can be severely debilitating and even fatal. For scuba diving there is an enormous literature on how to change water depth safely to avoid any possible DCS. Advice from such work emphasises that pressure changes should be very slow and involve significant periods of resting at intermediate depths. Here we consider a different regime where the possibility of DCS needs to be assessed when submariners have been exposed to raised pressure for a long time, and then undertake a highly transient pressure manoeuvre that arises when escaping from a submarine at very large depths. The purpose of the study group work was to consider models that might explain existing data and also give realistic predictions outside the scope of the existing data.

Scuba divers usually dive to depths no greater than 30m and may have to spend considerable time returning from this depth to the surface. The problems that they are attempting to avoid are caused by the pressure differences

at various depths. For every increase in depth of ten metres, the hydrostatic pressure and hence the pressure in a diver's breathing air, increases by one bar. The air in the lungs dissolves into the blood and is carried to the various tissues of the body. Oxygen is metabolised by the tissues but nitrogen is inert and remains in the tissues in dissolved form. Thus, the partial pressure or "tissue tension" of dissolved nitrogen in the tissues tends to equilibrate with that in the lungs over time. Once equilibrium is reached the tissue is said to be "saturated" at the nitrogen partial pressure. The rate at which this equilibration occurs depends crucially on the type of tissue and how well it is perfused by the blood. The most poorly perfused tissues may take 48 hours to reach saturation. However, the body is thought to be close to saturation within 24 hours at a given pressure. The transfer rates of gases from the blood to the tissue are different for different components of the air.[1]

If the nitrogen partial pressure in the blood is greater than that in the tissue then this will simply increase the rate at which nitrogen diffuses into the tissue, diffusion slowing as equilibrium is achieved and, in general, this creates no serious effects on the diver. Hence a diver can increase their depth as quickly as they wish. However, if the ambient pressure on the diver is lower than the tissue gas tension, gas bubbles can form in either the blood or the tissue and can cause a number of symptoms ranging from itchy skin (pruritis), through limb pain to central nervous system damage, lung oedema and death. Bubbles in the blood are generally thought be filtered out at the lungs, although it has been suggested that large bubble loads may overwhelm the lungs and pass to the arterial circulation where they may become trapped upon reaching the tissue capillaries. Bubbles may also pass to the arterial circulation via arteriovenous shunts. It is bubbles in the tissue or trapped in the tissues capillaries that are thought to be the dominant source of the symptoms of DCS. Hence a diver must ascend from depth in a regulated manner to avoid these complications.

The problem that the Study Group considered is where a submarine crew is in a submarine at raised air pressure and has been there for some time (typically a day or more) The air pressure in the submarine is assumed to be between sea-level (atmospheric pressure, 1.01325 bar Absolute or 0.0 bar Gauge) and up to three bar above this. We refer to the excess pressure in the submarine in bar above sea-level as the *Saturation Pressure*. Note that submarines typically operate with internal ambient pressure equal to sea-level pressure (so that *Saturation Pressure* equals 0bar) but we wish to consider other scenarios where the saturation pressure is increased. We wish

[1]There are additional complications if the air being breathed by the diver is not the same mixture as the regular atmosphere but this complication was not considered by the Study Group.

to assess the probability of the diver experiencing DCS if they then escape from the submarine. Such an escape is a highly transient event where the submariner is rapidly pressurized to the water pressure around the submarine before beginning the ascent. We shall refer to the pressure surrounding the submarine as the *Escape Depth* and this can vary from *Escape Depth* equal to 0bar at the surface to values around 40bar in severe cases. The submariner then travels upwards, at an almost constant speed, to the surface. The travel time from the submarine to surface is typically one to two minutes and during this time the submariner must breathe constantly to prevent the expanding air in the lungs from causing lung rupture. During the transient escape phase, which is short but extremely deep, further nitrogen will be absorbed into the submariner's tissues, which may also lead to DCS in addition to the nitrogen absorbed during the saturation phase. Assessing the possibility of the bends occurring due to the interacting effects of the Saturation Pressure, denoted S, and the Escape Depth, denoted E, was the aim of the Study Group. A particular goal of the work was to determine a contour plot for the risk of DCS occurring as a function of the two parameters S, E. Such a contour plot must be guided by and describe existing data.

In designing the model it is important to know what data are available to identify parameter values in the model. The data that exists describes the saturation pressure and escape depth to which subjects have been exposed in experimental trials. It also gives some basic information about the subject of the experiment such as body mass. The outcome of the experiment takes the form of a record of whether or not DCS occurred (a binary outcome), of the time after reaching the surface when the DCS first occurred and, in many cases, also the type of DCS that occurred (number of limbs affected or whether the central nervous system was affected *etc.*). Over 600 such records were available. It was therefore considered that the aim of the work should be to create a simple model that could give a robust description of the data and to avoid including large amounts of detail, as the data did not appear to merit this, showing quite large variability in outcomes for very similar experiments.

A number of approaches have been taken to this problem and the Study Group looked at a few of these as well as considering other ideas. One approach is a "black box" model where some suitable functional form is assumed for the probability of the bends occurring dependent on the saturation pressure and the escape depth; introducing free parameters in this function allows the model to be fitted to the data. A second approach is to exploit existing mechanistic models of the processes occurring during gas pressure changes in the submariner and to then incorporate a stochastic model of the bends occurring. By allowing some of the parameters in such models to be adjusted the data could then be fitted. In both cases the fitted

model can then be used to predict a contour map of the probability of the bends occurring. We shall discuss both of these approaches, although most effort was directed to the second approach.

2 Function fitting to the data

The first, and simplest approach, to explaining the data was to employ a regression analysis. The model used logistical regression where the probability of the bends occurring, which we denote by Prob(DCS), is assumed to depend on the parameters in the form

$$\log \frac{\text{Prob(DCS)}}{1 - \text{Prob(DCS)}} = \beta_0 + \beta_1 \text{S} + \beta_2 \text{E} + \beta_3 \text{ES} + \beta_4 \text{M}, \tag{1}$$

where S is the Saturation Pressure, E is the Escape depth and M is body mass. The constants β_1, β_2, β_3 and β_4 are free parameters. Such a model can be fitted to the simple binary data of whether the bends occurred or not by performing a maximum likelihood analysis.

3 Simple mechanistic model

There are many mathematical models of DCS which make different assumptions regarding the processes by which gases move into and out of the various tissues in the body. A very good review of these was given by G Loveman [1]. Given the detail of the data it was decided that a very simple version of such a model was appropriate for the purpose but that such a model should allow more detail to be included so that some assessment could be made of the balance between the number of parameters in the model and the accuracy of the data fitting.

The model of all parts of this process follows very closely the ideas, concepts and notation given in the paper by Thalmann, Parker, Survanshi & Weathersby [2]. The numerous tissue types within the body were assumed to be identified into a few compartments. Behaviour of gases within each compartment was assumed to be completely independent, so that more complex descriptions of transfers from blood to muscle to fat and so on were excluded. Each compartment was assumed to be well-mixed so that the behaviour can be adequately described by a temporal model involving ordinary differential equations. The arterial blood is assumed to be in very close contact with the air in the lungs so that it remains in equilibrium with surrounding atmosphere.

We assumed we had M independent compartments $i = 1, \ldots, M$ and that the partial pressure of nitrogen in each compartment is $N_i(t)$ (note that,

for simplicity, all pressures in this report are measured in bar gauge, that is, relative to sea-level pressure). Note that in more detailed models it is necessary to consider the effects of the metabolic gases but for simplicity and guided by previous work we assumed that the risk of DCS was dependent only on nitrogen super-saturation. Thus, for the work presented here, notational difficulties have been avoided by taking the blood to simply have a partial pressure of $N(t)$ as determined by the surrounding atmosphere.

For each compartment we need to consider the transfer of gas between the tissue the blood during decompression. While all the gas remains dissolved, there will be a transfer rate proportional to the difference in partial pressure between tissue and blood, resulting in exponential gas-kinetics. However, if a tissue is sufficiently super-saturated relative to the ambient pressure, it is assumed that a free-gas phase will form (a bubble) in the tissue compartment. This would significantly slow the removal of nitrogen from the tissue. It was reported (G. Loveman, private communication) that numerous mechanisms for representing this slowing have been used, including numerical solutions of bubble formation and growth and so on, but for simplicity here it was assumed that tissue-gas washout would follow exponential kinetics unless the supersaturation reached some limit for bubble formation above which the nitrogen washout rate was considered to be linear with time. Conservation of gas then dictates

$$\frac{dN_i}{dt} = \begin{cases} \dfrac{N - N_i}{\tau_i} & \text{if } \; N - N_i < P_i^{XO}, \\ \\ \dfrac{P_i^{XO}}{\tau_i} & \text{if } \; N - N_i \geq P_i^{XO}. \end{cases} \tag{2}$$

This model has two parameters, P_i^{XO} and τ_i. The latter is the response time of the tissue to fluctuation in the blood nitrogen pressure; specificlly tau_i is the half-time for nitrogen uptake and elimination while exponential kinetics are in effect, divided by ln(2). We anticipate that rapidly perfused tissue would have a small value for τ_i, perhaps measured in minutes, while less well perfused tissue, such as cartilage, would have a response of many minutes, if not hours. The parameter P_i^{XO} is the pressure difference beyond which the transfer rate becomes constant.

Equation (2) governs the behaviour in each compartment and we impose that initially the compartment will be in equilibrium with the saturation pressure, S. Hence we take

$$N_i(0) = S. \tag{3}$$

Finally we need to impose the nitrogen partial pressure in the subject's breathing air as the subject undergoes the ascent from the submarine. We

assume that the rate of rise is constant (which is typically around 3m s^{-1}) and that the pressure in the atmosphere is hydrostatic so that $U \approx 0.3$bar s^{-1}) and that the submarine is at an escape depth of E. Hence, taking $t = 0$ as the time when the subject leaves the submarine, the pressure will take the form

$$N(t) = \begin{cases} E - Ut & \text{if } 0 \le t < E/U, \\ 0 & \text{if } t \ge E/U. \end{cases} \tag{4}$$

Note that after $t = E/U$ the subject is at the surface and the atmosphere is at a pressure of 0.

3.1 Solution I: Purely exponenial gas kinetics ($P_i^{XO} \to \infty$).

If we suppopse that $P_i^{XO} \to \infty$, so that the resulting gas kinetics is purely exponential, then the solution for N_i is given by

$$N_i(t) = \begin{cases} (S - E - U\tau_i)e^{-t/\tau_i} + E - Ut + U\tau_i, & \text{if } 0 \le t < E/U, \\ \left[(S - E - U\tau_i)e^{-\frac{E}{U\tau_i}} + U\tau_i\right] e^{(\frac{E}{U} - t)/\tau_i}, & \text{if } t \ge E/U. \end{cases} \tag{5}$$

An example of the nitrogen partial pressure in the blood and the resulting pressure in a single compartment is given in figure 1.

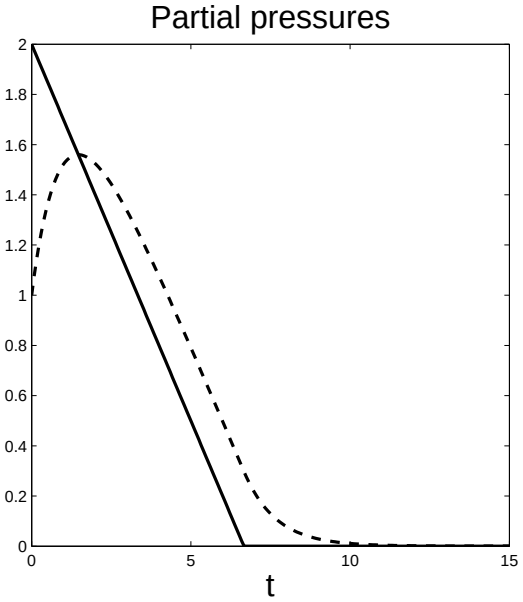

Figure 1: Typical nitrogen partial pressure in the blood and a tissue compartment for the case $P_i^{XO} \to \infty$. Here $S = 1$bar, $E = 2$bar, $U = 0.3$bar s^{-1} and $\tau_i = 1$s. Solid curve: $N(t)$; dashed curve: $N_i(t)$.

3.2 Solution II: Exponenial & linear gas kinetics (finite P_i^{XO}).

We now consider when P_i^{XO} is finite. If the values of S and E are then such that $E - S > P_i^{XO}$, then it is straightforward to show that the solution for N_i is

$$N_i(t) = \begin{cases} \frac{P_i^{XO}}{\tau_i} t + S, & \text{if } 0 \le t < t_1, \\ (E + U\tau_i - Ut) - (U\tau_i + P_i^{XO}) e^{-(t-t_1)/\tau_i}, & \text{if } t_1 \le t \le E/U, \\ \left[U\tau_i - (P_i^{XO} + U\tau_i) e^{-(E/U - t_1)/\tau_i}\right] e^{-(t-E/U)/\tau_i}, & \text{if } t > E/U, \end{cases} \tag{6}$$

where $t_1 = (E - S - P_i^{XO})/(U + P_i^{XO}/\tau_i)$. An example of the nitrogen partial pressure in the blood and the resulting pressure in a single compartment is given in figure 2.

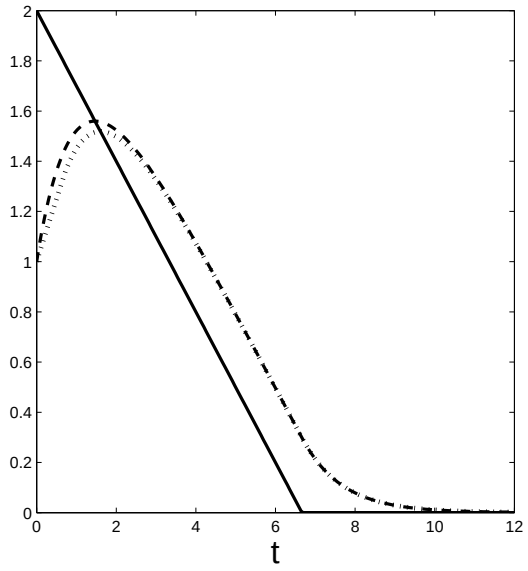

Figure 2: Typical nitrogen partial pressure in the blood and a tissue compartment for the case $P_i^{XO} = 0.5$bar. Here $S = 1$bar, $E = 2$bar, $U = 0.3$bar s^{-1} and $\tau_i = 1$s. Solid curve: $N(t)$; dashed curve: $N_i(t)$ from equation (5) ($P_i^{XO} \to \infty$); dotted curve: $N_i(t)$ from equation (6) ($P_i^{XO} = 0.5$bar).

4 Risk

In the previous section a model, that is partly based on known mechanisms, of the behaviour of gas pressures within tissue was described. For the next part of the modelling it is necessary to calculate if the bends would occur in

any specific case. The understanding of how DCS occurs and what creates the different responses between individuals and between experiments is, as yet, relatively unknown. As a results of this wide variability a stochastic approach was adopted.

Supersaturation of tissues over some threshold level above the ambient hydrostatic pressure drives bubble formation, hence, the presence of supersaturated tissues within the body may be taken as conferring some risk of DCS upon the individual. If the tissue nitrogen partial pressure is less than the hydrostatic pressure there can be no risk of the bends. A reasonable model is that when the difference between the tissue pressure and the blood pressure exceeds a threshold level (denoted here by N_i^{thresh}) then there will exist an instantaneous risk of DCS. The level of instantaneous risk depends, inversely on the ambient hydrostatic pressure. Hence the degree of risk of the bends occurring in any particular tissue was taken as

$$r_i = g_i \left(\frac{N_i(t) - N(t) - N_i^{\text{thresh}}}{N(t) + 1} \right)^+, \tag{7}$$

where the parameter g_i is referred to as the *gain* and may be taken to represent the sensitivity of the tissue to the pressure difference. (Also in this formula is the expression $N(t) + 1$ which represents the total atmospheric pressure which is $N(t)$ plus 1 bar.)

To illustrate how the risk changes during a particular escape sequence a plot of the excess pressure in the tissue $N_i(t) - N(t)$ is shown in in Figure 3 along with a threshold pressure.

Given this approximation for the risk of DCS, it is then assumed that the bends is a Poisson process with all tissues acting independently. The probability of the bends occurring in any time interval $[t_1, t_2]$ is then given by

$$\text{Prob(DCS)} = 1 - \exp\left(-\sum_{i=1}^{M} \int_{t_1}^{t_2} r_i \, dt \right). \tag{8}$$

Hence, because the data is primarily of the form where the bends is a binary outcome we can take that the probability of the bends occurring in any experiment is given by

$$\text{Prob(DCS)} = 1 - \exp\left(-\sum_{i=1}^{M} \int_{0}^{\infty} r_i \, dt \right). \tag{9}$$

Note that what we call the risk here is better known in statistical survival analysis as the hazard function. It represents the failure conditional probability density (failure rate) at time t conditional on survival up to that time.

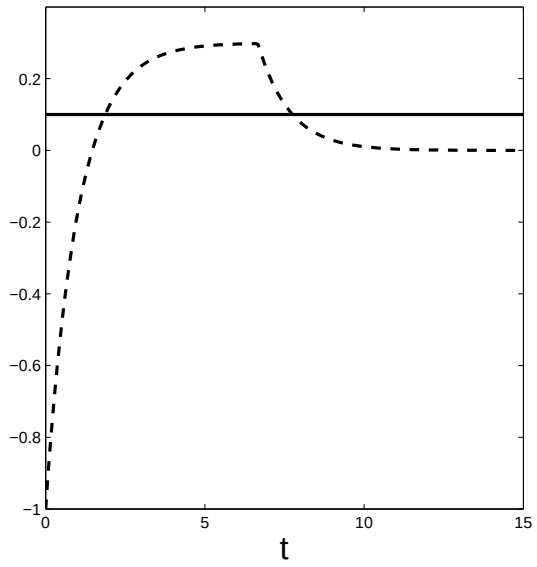

Figure 3: An example of the excess pressure in tissue ($N_i(t) - N(t)$) and the threshold pressure during an ascent. Here $P_i^{XO} \to \infty$, $N_i^{\text{thresh}} = 0.1\text{bar}$, $S = 1\text{bar}$, $E = 2\text{bar}$, $U = 0.3\text{bar s}^{-1}$ and $\tau_i = 1\text{s}$. Solid curve: N_i^{thresh}; dashed curved: $N_i(t) - N(t)$.

The fact that the cumulative (integrated) hazard is finite implies long-term survivors (subjects who do not get the bends).

5 Preliminary results

Number of compartments	M
Escape depth	E
Saturation pressure	S
Rate of ascent	U
Response time	τ_i
Threshold pressure for bubble formation	P_i^{XO}
Gain	g_i
Threshold pressure	N_i^{thresh}

Figure 4: Table of parameters.

The model outlined above was considered as a possible explanation of the existing experimental data. In fitting this model to the data we note that in summary the probability of the bends occurring depends on the parameters

given in table 4.

The number of compartments was chosen, and the constant U was specified. The model was then fitted to the experimental data to determine τ_i, P_i^{XO}, g_i and N_i^{thresh}. The model was then used to make predictions for the different values of E and S. As with the function fitting models described earlier here the parameters in the model were determined by using a maximum likelihood procedure. Note that at this initial stage the effects of body mass were not included.

This gives a large number of parameters and so initial attempts only considered a few compartments. Initially additional assumptions were made, such as the threshold parameters for gas transfer and excess tissue pressure, P_i^{XO} was taken as infinite and N_i^{thresh} was taken as zero but this gave a poor fit to the data, even just along the axes of E and of S.

A three compartment model was then considered, this was the optimal model number of compartments determined against a different dataset as described in [2], although further testing is needed here to determine the most parsimonious model for the current dataset. Various starting guesses were used for the parameters and results so far suggest that only two of the three original compartments are required to contribute significantly to the probability DCS. The results of these calculations are summarised in Figure 5 which shows the resulting contour maps of the probability as dependent on the parameters S and E.

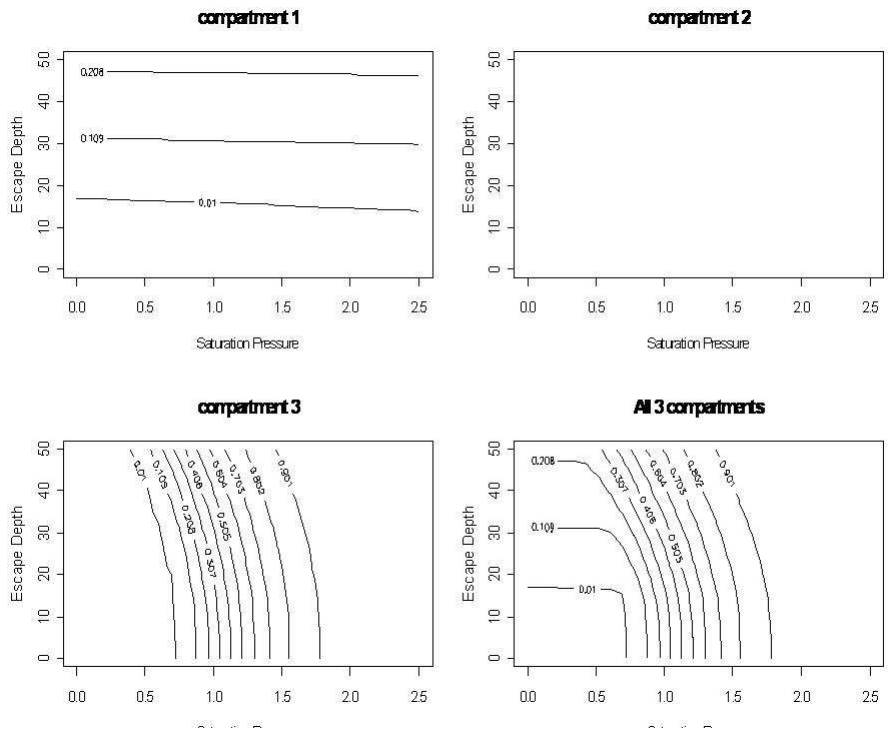

Figure 5: A plot of probability contours for a model fitted to existing data and containing three compartments.

6 Future work

Two extensions to the model were discussed. The first was that the model fitting might be extended by considering the effect of the body mass of the subject on the resulting probability of the DCS. It is known that tissue perfusion rates are dependent on body mass and the experimental data give some indication that results of any experiment might vary with different body mass. The suggestion was that the parameters tau_i, P_i^{XO}, g_i and N_i^{thresh} (and particularly the parameters τ_i which are so closely related to perfusion) are assumed to be linear functions of body mass, with unknown coefficients, in the spirit of a regression procedure. These coefficients would then be determined in the same manner as above.

The second suggestion was that there are some mechanisms that are important in determining the onset of the DCS that are not included in the mechanistic model that is outlined here. In such cases it would be appropriate to consider a hybrid model where the mechanistic probability and the "black box" probability are amalgamated as independent risks. This has yet

to be pursued.

One other area of discussion considered the fitting procedures used to determine the parameters in the model. Here a frequentist approach has been adopted with probabilities predicted and the model fitted. It might however by preferable to incorporate other information in a more systematic manner. This for example might include data concerning transfer rates of the gases as determined from other experiments or information about possible tissue damage resulting from pressure differences. These could be included if a Bayesian approach were taken. To calculate posterior modes as Bayesian point estimates could be achieved with approximately the same computational effort as the current procedure. However, a Bayesian approach offers the potential of obtaining realistic quantification of parameter uncertainty, and integrating uncertainty into predictions. To do a full Bayesian analysis in this way is likely to more computationally demanding – Markov chain Monte Carlo would be an obvious computational approach to try; the dimensionality of the model is not so large that such an approach would be likely to be prohibitive. Taking this one step further, ideally the approach would also allow for model uncertainty, particularly concerning the number of compartments. Letting the data determine this, and quantifying the associated uncertainty adds a further level of computational complexity.

References

[1] Loveman,G., private communication.
[2] Thalmann,E.D., Parker,E.C., Survanshi,S.S. & Weathersby,P.K. "Improved probabilistic decompression model risk predictions using linear-exponential kinetics." *Undersea Hyperbar. Med.* **24**, 255-274, 1997.