31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

A Three-State Non-Linear Model of Vascular Nitric Oxide Transport

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Abstract—**Nitric Oxide (NO) plays a crucial role in the regulation of blood flow around the body. Biological experiments have shown that blocking NO production induces vasomotion, which is caused by instabilities in blood vessel walls. It has been suggested that the observed vasomotion on NO blockade is because a NO flow dependent system is actually stabilised by the myogenic system, since the coupling together of two unstable mechanisms can enable a system to become stable. We thus propose here a model for the interaction between flow and NO production, with a flow feedback mechanism and analyse its stability both numerically and analytically. We show that the presence of flow feedback introduces instability, which thus provides the basis for a more detailed model of the autoregulation response, when coupled with a model of the myogenic response, and derive a result for the oscillation frequency of the system.**

I. Introduction

THE modeling of NO has been an active area of research ever since its vital role in the regulation of blood flow was first realised. An adequate and continuous blood supply is a vital mechanism for homeostasis. The first models of NO transport were developed by Lancaster (see for example Lancaster, 1997), with it being shown that the concentration of NO in the bloodstream is strongly influenced by the flow of blood through the vessel. This can be termed the NO-flow dependent system (Buerk, 2001).

Biological experiments in rat cerebral arteries (Lacza et al., 2001) show that blocking the production of NO induces chaotic vasomotion. Vasomotion represents spontaneous rhythmic changes of the vessel diameter, the introduction of a NO donor causes which to cease. It is thought that vasomotion may be produced because of instabilities in the myogenic response, originally proposed by (Bayliss, 1902). A number of models have thus been proposed to simulate the oscillations caused by vasomotion, for example (Gonzalez and Ermentrout, 1994), (Parthimos et al., 1999) and (Marsh et al., 2005). However, there are several mechanisms that interact, making analysis difficult, particularly with regard to its stability. One hypothesis, which we partially explore here, is that the observed vasomotion on NO blockade is because there is a NO flow dependent system which is actually stabilised by the myogenic system, as discussed by (Marsh, 2005).

This arises from the fact that the coupling together of two unstable control systems can result in a stable system. For example, a dither is a high-frequency signal introduced into a system with the object of modifying its nonlinear characteristics. By dithering a system it is possible to augment stability, quench undesirable limit-cycles, and reduce nonlinear distortion under a wide range of conditions (Zames and Sneydor, 1976). The removal of either one of these aspects can make a dithered stable system unstable. In this paper we develop a simple model for the flow dependent NO behaviour and analyse its stability. This provides the first step in the construction of a coupled myogenic / flow dependent NO model, which will be invaluable in understanding better the processes that govern the autoregulation of blood flow.

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II. Theory

To explore the role of NO, we consider here its interaction with the blood vessel wall, and hence the vessel cross-sectional area, and flow rate. Although this considers the wall to be purely a passive medium, it provides a first step in understanding the key pathway of NO and its behaviour. The myogenic response is not considered here since the focus is solely on the NO-flow dependent system. The myogenic response and its coupling with the flow dependent system will be considered separately. The general mass transport equation is presented first, as this provides the basis for NO behaviour, before considering the relationship between NO and radius and finally between radius and flow. The full model is then presented before its behaviour is analysed.

A. Mass Transport Equation

NO concentration in the bloodstream is governed by the general mass transport equation:

$$\frac{\partial C_{NO}}{\partial t} + \mathbf{U}.\nabla C_{NO} = D\nabla^2 C_{NO} + R_{NO}, \quad (1)$$

where NO concentration, C_{NO}, is dependent upon the local velocity field, $\mathbf{U}$, the diffusion coefficient, D, and the local reaction rate, R_{NO}. In blood vessels, NO concentration is usually assumed to be circumferentially symmetric and is thus a function of three parameters: distance along the x-axis; change in radial distance, r, and time, t. Convection in the axial direction is frequently neglected and the steady state solution can then be determined analytically as a function of radius if the reaction rate is known (Buerk, 2001). Since solving the full diffusion-reaction-convection equation, is very complicated and dependent upon the boundary and initial conditions, a much simpler approach is adopted here to perform an initial investigation into the system stability.

To remove the geometrical variations, equation 1 is volume averaged and referenced to steady state values of concentration and flow. Diffusion is thus neglected and the reaction is assumed linearly proportional to concentration. Equation 1 thus reduces to a first order form:

$$\tau_c \frac{dC}{dt} + \beta^*(q - \bar{q})C = (\overline{C} - C), \quad (2)$$

where *C* denotes the volume averaged concentration of NO in a single blood vessel. Note that, as flow increases, it sweeps out more NO, thus reducing *C*. The concentration thus reduces as the flow increases; for simplicity, we assume a linear dependence on flow, as implied by equation 1.

NO concentration and axially averaged flow, *q*, are both defined relative to their baseline values, denoted by the overbar. Equation 2 is a very simplified form of equation 1 with being dependent upon time only and diffusion being neglected. The time constant, τ_c, and feedback parameter, β^*, can be determined from the full solution of the convection-diffusion-reaction equation, but are assumed here to have fixed values for simplicity. The effects of variations in these parameters on the model behaviour will be examined later.

B. Vasodilation

The effect whereby the vessel's radius increases to meet the tissue's requirement for elevated blood flow, vasodilatation, is widely acknowledged. For simplicity we assume here that the vessel radius, *R*, increases with *C* due to vasodilatation, again in a first order linear manner:

$$\tau_R \frac{dR}{dt} = R_t - R, \quad (3)$$

where:

$$\frac{R_t}{\overline{R}} - 1 = \alpha\left(\frac{C}{\overline{C}} - 1\right), \quad (4)$$

Note that the 'target' vessel radius, R_t, is set by the volume-averaged level of NO to adjust the tissue's required flow level and feedback parameter α. The vessel radius responds to this 'target' value with time constant τ_R, mimicking the behaviour of the vessel wall as a visco-elastic medium. Although the parameters in this part of the model can be determined by experimental measurement, they will vary from vessel to vessel and under different pathological states. The effect of variations in these parameters will thus be examined later.

C. Flow Coupling

In order to complete the feedback mechanism between NO concentration and radius, the relationship between radius and flow must be included. For steady state linear flow in a rigid vessel, the Poiseuille equation holds. However, the flow has inertia as well as friction. We thus mimic this using the well established concepts of resistance and inductance in an equivalent electrical circuit as:

$$\Delta p = R_s q + I\frac{dq}{dt}, \quad (5)$$

which, in non-dimensional form, given that resistance is inversely proportional to vessel radius to the power 4, yields:

$$\tau_f \frac{df}{dt} = -f + r^4, \quad (6)$$

where $f = q/\overline{q}$ and Δp is assumed constant. The time constant, τ_f, is equal to the ratio of inertia to resistance for the vessel. For vessels of diameter 1 mm, it is of order 1 second (Wilmer and Rourke, 1998), although it will vary from vessel to vessel. Its precise value can be calculated from solutions of the full axi-symmetric Navier-Stokes equations. Note that the flow equation is very strongly nonlinear, as is equation 2, due to the resistance being a function of radius to the fourth power. This nonlinearity is important since nonlinear interactions can give rise to a number of interesting system properties, including chaos, synchronization, and frequency modulation, which may be physiologically important, and which cannot occur in linear systems.

D. Full Model Equations

The model is thus described in a non-dimensional form by three non-linear coupled equations:

$$\tau_c \frac{dc}{dt} = (1 - c) - \beta c(f - 1), \quad (7)$$

$$\tau_R \frac{dr}{dt} = (1 - r) + \alpha(c - 1), \quad (8)$$

$$\tau_f \frac{df}{dt} = -f + r^4. \quad (9)$$

where non-dimensional NO concentration and vessel radius are given as $c = C/\overline{C}$ and $r = R/\overline{R}$ respectively. The model has three time constants: τ_c, τ_R and τ_f; and two feedback parameters: α and β. There are two non-linear effects: the product of concentration and flow in equation 7 and the radius to the fourth power in equation 9. Before analysis of the model behaviour is presented, the results from some numerical simulations are presented in the next section to illustrate the behaviour of the model. In particular, the effects of both feedback parameters on the model behaviour are investigated.

III. Numerical Simulations

The full NO model is simulated using Matlab's differential equation solver, ode15s, for a range of values for the model feedback parameters, all the time constants initially being set to one second for simplicity. The initial state of the model is taken to be somewhat perturbed from its steady state condition: it was found that the resulting behaviour is not

influenced by this initial condition, however, within a wide range of values. Figures 1 and 2 show the change in concentration, radius and flow with respect to non-dimensional time for two combinations of the feedback

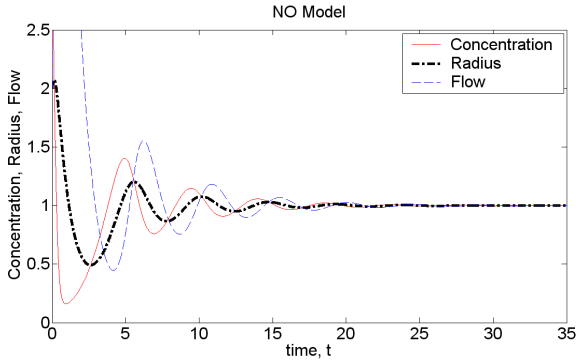

Fig. 1. Model simulations for $\alpha = 1; \beta = 1$.

parameter values.

In the first case, the model settles back into its stable state, $(1,1,1)$, but in the second, it settles into oscillatory behaviour about this point. It is found numerically that sustained oscillations occur when the product of α and β is equal to or greater than 2. As this product increases above this threshold, the oscillations increase in amplitude due to the strong nonlinearity of the model. The model behaviour appears to be determined largely by the product of α and β. The shape of oscillations is also not very sinusoidal for large α and β values: again due to the strong non-linearity in the model. In practice such large oscillations will not be seen since the linear radius/concentration equation is likely to saturate strongly at extreme values, something that we do

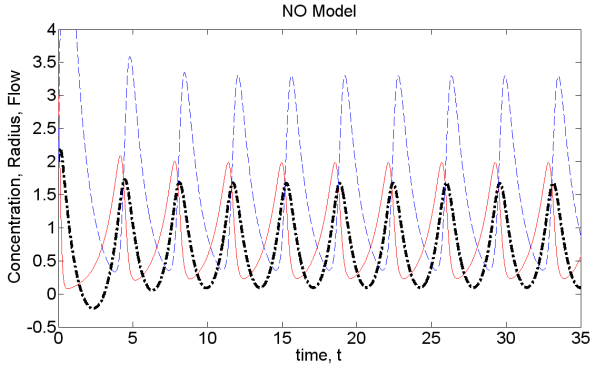

Fig. 2. Model simulations for $\alpha = 2; \beta = 2$.

not consider in this model at this stage. It is also found that the frequency of oscillations seems to be fairly constant with both α and β.

IV. Analysis

In this section the stability of the NO model is examined first before the necessary condition for the existence of a limit cycle in the model is derived. An approximate analytical solution for the frequency of oscillation is then derived and compared with the true solution. Note that only the frequency is examined here, for two reasons: firstly that physiologically this is the parameter of greater interest and secondly the amplitude predicted by this model seems to be a significant overestimate.

The linearised NO model about this equilibrium point can be written in the form:

$$\frac{d}{dt}\begin{pmatrix} c \\ r \\ f \end{pmatrix} = A_3 \begin{pmatrix} c \\ r \\ f \end{pmatrix}, \quad (10)$$

where A_3 is given as:

$$A_3 = \begin{bmatrix} -\frac{1}{\tau_C} & 0 & -\frac{\beta}{\tau_C} \\ \frac{\alpha}{\tau_R} & -\frac{1}{\tau_R} & 0 \\ 0 & \frac{4}{\tau_f} & -\frac{1}{\tau_f} \end{bmatrix}. \quad (11)$$

The eigenvalues of equation 11 are then found from the solution to:

$$\lambda^3 + \left(\frac{1}{\tau_c} + \frac{1}{\tau_R} + \frac{1}{\tau_f}\right)\lambda^2 + \left(\frac{1}{\tau_c\tau_R} + \frac{1}{\tau_c\tau_f} + \frac{1}{\tau_R\tau_f}\right)\lambda + \left(\frac{1+4\alpha\beta}{\tau_C\tau_R\tau_f}\right) = 0 \quad . (12)$$

Since the general solution is very complicated, we only consider the case here where all the time constants are equal. Equation 12 then reduces to:

$$\lambda^3 + \frac{3}{\tau}\lambda^2 + \frac{3}{\tau^2}\lambda + \frac{1+4K}{\tau^3} = 0, \quad (13)$$

where $K = \alpha\beta$. The eigenvalues are thus:

$$\lambda_{1,2} = \frac{1}{\tau}\left(-1 + \sqrt[3]{\frac{K}{2}} \pm i\sqrt{3}\sqrt[3]{\frac{K}{2}}\right), \quad (14)$$

$$\lambda_3 = -\frac{\left(1+\sqrt[3]{4K}\right)}{\tau}. \quad (15)$$

The eigenvalues $\lambda_{1,2}$ can thus have a positive real part, which is a necessary, although, not sufficient condition for a limit cycle to exist. Note that λ_3 is always negative. Since the real part of $\lambda_{1,2}$ is positive when $K > 2$, the full NO model has a unstable equilibrium point when the product of α and β is greater than 2, in agreement with the numerical simulations. This indicates that the individual values of α and β are not of importance, only their product. Note that the full NO model is linearised about its equilibrium point

here and thus its behaviour can only be approximated in this manner in the vicinity of its equilibrium point.

A Fourier based approach is adopted here to obtain an approximate analytical solution of the frequency of oscillation. The radius, *r*, is thus assumed to have the following approximate form:

$$r(t) = 1 + A\cos(\omega t), \quad (16)$$

where A is the approximate amplitude and ω is the approximate frequency of oscillation. To derive an expression for ω, the full NO model (equations 7, 8 and 9) is used in linearised form. First, substitute equation 16 into equation 8 and then substitute the resulting expression into equation 7. Finally, equating the cosine and sine terms to zero in equation 9 (Jordan and Marshall, 1999) and eliminating αβ, gives:

$$\omega^2 = \frac{\tau_C + \tau_R + \tau_f}{\tau_C \tau_R \tau_f}. \quad (17)$$

If all the time constants are equal, then $\omega^2 = 3/\tau$. Note that this result for frequency is independent of α and β. The plot of actual frequency of oscillation, taken from the numerical simulations, with respect to αβ for both β=1 and β=2 with all time constants equal to 1 second is shown in Figure 3.

The theoretical prediction is in good agreement with the numerical results, the maximum error between theoretical and simulation results being less than 5%. Given the very approximate nature of this model, this seems to be a very useful result for frequency. Note that the frequency is determined by all 3 time constants equally. If one time constant is much smaller than the other two, then the resonant frequency becomes very large, i.e. the oscillations become very slow. In the limit as one of the time constants tends to zero, the frequency tends to infinity, i.e. the oscillations disappear.

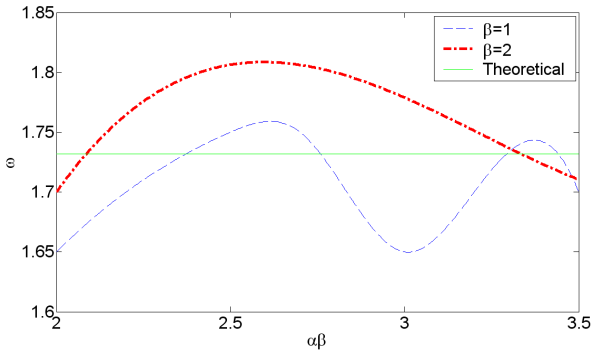

Fig. 3. Frequency of oscillations: theoretical prediction against numerical simulation results

V. Conclusion

We have presented a very simple, yet effective, model for the instability in the flow-NO coupled system. However, since NO will obviously vary in both space and time, a more detailed model will be required. This will also be valuable in determining the values of the feedback parameters and time constants, which are as yet unknown in the context of this model. The effect of pressure changes on the stability of model thus will be examined in a separate paper, to investigate the coupling between oscillations in pressure and radius/concentration. In particular, any forced oscillations could prove to be of considerable importance. We then plan to link this model to a myogenic model to investigate the stability of the coupled system.

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