A MATHEMATICAL MODEL OF SEDIMENTATION AND RESUSPENSION PHENOMENA RELATED TO ATHEROSCLEROSIS DEVELOPMENT

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SUMMARY – A mathematical model simulating the development of atheroma is presented. The model takes into account both possible sedimentation and resuspension phenomena occurring between atheromatic plaque and blood, following the stochastic processes theory, in which interactions may be studied as a case of a Yule-Furry process. The calculated expected value for the sedimented particles and the variance analysis are also given. The main results show that the growth of the plaque is strongly influenced by the values of the sedimentation and resuspension parameters, whereas the variance of the whole phenomenon seems to indicate the time interval in which a pharmacological approach may be more effective.

KEY-WORDS: Atheroma, Sedimentation and resuspension, Stochastic processes theory.

INTRODUCTION

The development of atheroma seems to have a basic relevance in order to clarify the role of all lipoproteins involved in the development of hiscaemic heart disease. Some hypotheses about the deposition and remotion of the particles forming the atheroma have been discussed, for example, by Lee (1985). Many aspects of the global phenomenon are, on the other hand, still unclear, enclosing the physiopatological mechanism determining the deposition itself, and inducing the initial sign of the plaque, also observed in the newborn babies.

It is also known that the plaque is the result of a focal artery lesion given by a strongly heterogeneous mixture of lipids, cells and proteins. The cause may be phenomenologically described as an interaction of crculating lipoproteins with the endotelial cells of artery vessels.

The atherogenesis is a slowly evolving proliferative process depending on many variables (risk factors) having different origin (i.e. hereditary characters, life style and smoke habits, and other); the chronic phase of the disease is followed by an acute phase determined by the obstruction of an artery and interesting some organs (particularly the heart). The slow phase of atheroma growth may be regarded as a sedimentation-like process and, moreover, taking into account the great number of particles involved in the whole phenomenon, the sedimentation

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of a given particle is to be regarded as random, so that the sedimentation of a population of particles may be studied as a stochastic process.

Descovich and co-authors (1987, 1989) and Nichelatti and co-authors (1990, a) proposed a mathematical model based on the Markov birth processes theory in order to study the evolution of the atheromatic plaque as the result of a pure sedimentative phenomenon; on the other hand, Malinow and Blaton (1984) described the real possibility of a regression of the atheromatic lesions, and therefore a more complete mathematical model involving also the resuspension of sedimented particles may be justified.

MODEL

The model starts from the following assumptions: a) the number n of sedimented particles must be less than m, the number of particles covering an entire cross section of a given artery: b) at initial time the number n_0 of already sedimented particles is known: it can be equal at least to zero; c) knowing at time t the exact number of sedimented particles, the sedimentation at time $t' > t$ will evolve independently on the process before t.

The evolution of the size of atheroma will take into account the interaction of simultaneously occurring sedimentation and resuspension and will be considered a case of Yule-Furry processes, as described by Nichelatti and co-authors (1990, b).

On the basis of the above assumptions, the probability generating function related to the problem may be written as

$$\Psi(s,t) = \sum_{n=0}^{\infty} s^n \, P\{N = n, t\}, \tag{1}$$

with the boundary condition $\Psi(s, t|t = 0) = s^n$. In the above equation s represents the independent variable of the process (a parameter useful for mathematical elaboration but without physical meaning), whereas N is the random variable of the whole phenomenon.

Considering the total probability, in which all terms containing "small-oh" have been neglected, one can write

$$\begin{aligned} P\{N = n, t + \Delta t\} = {} & S(n-1)\Delta t \, P\{N = n-1, t\} + R(n+1)\Delta t \, P\{N = n+1, t\} \\ & + \{1 - S(n)\Delta t - R(n)\Delta t\} \, P\{N = n.t\}, \end{aligned} \tag{2}$$

in which $S(n)$ is the sedimentation intensity function, and $R(n)$ is the remotion intensity function. These last may be rewritten in terms of sedimentation and resuspension parameters (λ and β respectively), to have

$$S(n) = (m - n)\lambda \quad ; \quad R(n) = n\beta, \tag{3}$$

and also dividing both sides of equation (2) by Δt, and passing to the limit $\Delta t \to 0$, one can obtain the following system of ordinary differential equations:

$$\frac{dP\{N=n,t\}}{dt} = S(n-1)P\{N=n-1,t\} + R(n+1)P\{N=n+1,t\} - \{S(n)+R(n)\}P\{N=n,t\}. \tag{4}$$

Comparing equations (1) and (4), we can write

$$\sum_{n=0}^{\infty} s^n \frac{dP\{N=n,t\}}{dt} = \sum_{n=0}^{\infty} s^n \{m-(n-1)\}\lambda P\{N=n-1,t\} + \sum_{n=-1}^{\infty} s^n (n+1)\beta P\{N=n+1,t\} - \sum_{n=0}^{\infty} s^n \{(m-n)\lambda + n\beta\}P\{N=n,t\}, \tag{5}$$

and, in terms of generating function,

$$\frac{\partial}{\partial t}\sum_{n=0}^{\infty} s^n P\{N=n,t\} = \lambda m s \sum_{n-0}^{\infty} s^{n-1} P\{N=n-1,t\} + \beta \frac{\partial}{\partial s}\sum_{n=-1}^{\infty} s^{n+1} P\{N=n+1,t\} + \lambda s \frac{\partial}{\partial s}\sum_{n=0}^{\infty} s^n P\{N=n,t\} - \lambda s^2 \frac{\partial}{\partial s}\sum_{n=0}^{\infty} s^{n-1} P\{N=n-1,t\} - \lambda m \sum_{n=o}^{\infty} s^n P\{N=n,t\} - \beta s \frac{\partial}{\partial s}\sum_{n=0}^{\infty} s^n P\{N=n,t\}, \tag{6}$$

from which one can obtain

$$\frac{\partial \Psi(s,t)}{\partial t} = m\lambda(s-1)\Psi(s,t) - (s-1)(\lambda s+\beta)\frac{\partial \Psi(s,t)}{\partial s}. \tag{7}$$

EXPECTED VALUE

Equation (7) represents, also considering equation (1) and the boundary conditions, the Cauchy problem related to the phenomenon: using the method of characteristics, we can obtain the final form for the generating function, written as follows:

$$\Psi(s,t) = \left[\frac{\lambda s + \beta}{\lambda + \beta}\right]^m \left[1 - \lambda \frac{s-1}{\lambda s + \beta} \exp\{-(\lambda+\beta)t\}\right]^{m-n} \times \left[1 + \beta \frac{s-1}{\lambda s + \beta} \exp\{-(\lambda+\beta)t\}\right]^n \tag{8}$$

The first derivative of $\Psi(s,t)$ with respect to s may be calculated from equation (8) as follows:

$$\begin{aligned}\frac{\partial \Psi(s,t)}{\partial s} = \frac{1}{(1+\beta/\lambda)^m} \Bigg\{ & m(s+\beta/\lambda)^{m-1} \left[1 - \frac{s-1}{s+\beta/\lambda} \exp\{-(\lambda+\beta)t\}\right]^m - n \\ & \times \left[1 + \beta/\lambda \frac{s-1}{s+\beta/\lambda} \exp\{-(\lambda+\beta)t\}\right]^n - (m-n)(1+\beta/\lambda)(s+\beta/\lambda)^{m-2} \\ & \times \left[1 - \frac{s-1}{s+\beta/\lambda} \exp\{-(\lambda+\beta)t\}\right]^{m-n-1} \left[1 + \beta/\lambda \frac{s-1}{s+\beta/\lambda}\right. \\ & \times \left. \exp\{-(\lambda+\beta)t\}\right]^n \exp\{-(\lambda+\beta)t\} + n\beta/\lambda(1+\beta/\lambda)(s+\beta/\lambda)^{m-2} \\ & \times \left[1 - \frac{s-1}{s+\beta/\lambda} \exp\{-(\lambda+\beta)t\}\right]^{m-n} \left[1 + \beta/\lambda \frac{s-1}{s+\beta/\lambda}\right. \\ & \times \left. \exp\{-(\lambda+\beta)t\}\right]^{n-1} \exp\{-(\lambda+\beta)t\} \Bigg\}\end{aligned} \tag{9}$$

The expected value for the particles is also

$$\begin{aligned} E\{N(t)\} &= \left.\frac{\partial \Psi(s,t)}{\partial s}\right|_{s=1} \\ &= \frac{m}{1+\beta/\lambda} + \frac{(\lambda+\beta)n - \lambda m}{\lambda+\beta} \exp\{-(\lambda+\beta)t\}. \end{aligned} \tag{10}$$

All the possible graphs of $E\{N(t)\}$ versus t are strongly influenced by the λ and β values: in particular it may be easily proved that in a given point of an artery interested to atheroma, if sedimentation and resuspension are simultaneously occurring, the sedimentation is prevailing if $n(1+\beta/\lambda) > m$, while the resuspension prevails if $n(1+\beta/\lambda) < m$. The cases of pure sedimentation (i.e. $\beta \to 0$) and pure resuspension (i.e. $\lambda \to 0$) may be evolved from equation (10).

The physical meaning of both λ and β parameters is to describe the "metabolic efficiency" of the particles to sedimentate on the surface of the atheroma and to return into blood stream respectively: this ability is dimensionally a frequency (λ and β are to be measured in Hertz), which roughly gives us an idea of the number of particles moving from blood stream to atheromatic plaque and vice-versa. It is to note that, at present, the model does not consider the number of circulating lipid particles: this is mainly due to necessity to maximally simplify the mathematical procedures in order to assess and to improve the model itself, but it may also

have a biological significance. The atherosclerosis and its clinical consequence have been described also in subjects having the values of cholesterol-rich lipoproteins (predominantly LDL and VLDL) and of triglycerides-rich lipoproteins (chylomicrons) in a range of apparent safety. This implies that atherosclerosis may be induced by habits and life-style factors but also by a genetically-governed etiology, in which the number of circulating particles may be small, but the value of λ may be very high.

VARIANCE ANALYSIS

The variance $\mathrm{Var}\{N(t)\}$ of the considered stochastic process may be written, in terms of generating function, as follows:

$$\mathrm{Var}\{N(t)\} = \left.\frac{\partial^2 \Psi(s,t)}{\partial s^2}\right|_{s=1} + \left.\frac{\partial \Psi(s,t)}{\partial s}\right|_{s=1} - \left\{\left.\frac{\partial \Psi(s,t)}{\partial s}\right|_{s=1}\right\}^2 \tag{11}$$

Squaring equation (10) one obtain

$$\begin{aligned}\left\{\left.\frac{\partial \Psi(s,t)}{\partial s}\right|_{s=1}\right\}^2 = \left[\frac{m}{1+\beta/\lambda}\right]^2 &+ \frac{2mn(1+\beta/\lambda) - m^2}{(1+\beta/\lambda)^2}\exp\{-(\lambda+\beta)t\} \\ &+ \frac{n^2(1+\beta/\lambda)^2 - 2mn(1+\beta/\lambda) + m^2}{(1+\beta/\lambda)^2}\exp\{-2(\lambda+\beta)t\},\end{aligned} \tag{12}$$

whereas the second derivative of Ψ vs. s is as follows:

$$\begin{aligned}\left.\frac{\partial^2 \Psi(s,t)}{\partial s^2}\right|_{s=1} = &\frac{2(m-1)[n(1+\beta/\lambda) - m]}{(1+\beta/\lambda)^2}\exp\{-(\lambda+\beta)t\} \\ &+ \frac{(m-n)(m-n-1) - 2(m-n)n\beta/\lambda + n(n-1)(\beta/\lambda)^2}{(1+\beta/\lambda)^2} \\ &\times \exp\{-2(\lambda+\beta)t\};\end{aligned} \tag{13}$$

hence, taking into account equations (11), (10), (12) and (13), the variance assumes the form

$$\begin{aligned}\mathrm{Var}\{N(t)\} = &\frac{m\lambda\beta}{(\lambda+\beta)^2} + \frac{(m-n)\lambda^2 - m\lambda\beta + n\beta^2}{(\lambda+\beta)^2}\exp\{-(\lambda+\beta)t\} \\ &- \frac{(m-n)\lambda^2 - n\beta^2}{(\lambda+\beta)^2}\exp\{-2(\lambda+\beta)t\}.\end{aligned} \tag{14}$$

From equation (14) one can evolve that

$$\mathrm{Var}\{N(t|t=0)\} = 0, \tag{15}$$

and

$$\mathrm{Var}\{N(t|t=\infty)\} = \frac{m\lambda\beta}{(\lambda+\beta)^2} \stackrel{\mathrm{def}}{=} W(\lambda,\beta), \tag{16}$$

so that the variance of the phenomenon will increase till their maximum value, corresponding to time

$$\vartheta_{MAX} = \frac{1}{\lambda + \beta} \ln \left\{ \frac{2[(m-n)\lambda^2 - n\beta^2]}{(m-n)\lambda^2 - m\lambda\beta + n\beta^2} \right\}, \tag{17}$$

also decreasing till the value given by equation (16).

It may be interesting to analyze the function $W(\lambda, \beta)$, defined in equation (16), and describing the behavior of $\mathrm{Var}\{N(t)\}$ when time t tends to infinity. Taking into account the matrix

$$Z = \begin{vmatrix} \frac{\partial^2}{\partial\lambda^2} W(\lambda,\beta) & \frac{\partial^2}{\partial\lambda\partial\beta} W(\lambda,\beta) \\ \frac{\partial^2}{\partial\beta\partial\lambda} W(\lambda,\beta) & \frac{\partial^2}{\partial\beta^2} W(\lambda,\beta) \end{vmatrix} \tag{18}$$

their determinant $\det\{Z\}$ will assume the value

$$\det\{Z\} = -m^2 \frac{(\lambda^2 - \beta^2)^2}{(\lambda + \beta)^8}, \tag{19}$$

hence $W(\lambda, \beta)$ does not have extremum points for every positive value of the λ and β parameters, being m a positive number by definition.

DISCUSSION AND CONCLUSIONS

The application of mathematical techniques to the study of atherosclerosis is at present only at the starting point: a limitation is given by the great number of uncertainties which remain at the basis of the metabolic hypotheses about the plaque birth; the same management of data evolving from "in vitro" and "in vivo" studies is often very difficult for the fast growth of knowledges in these last years.

The present model is actually very simple with respect to the real situation, but the main results seem indicate some facts which may have some relevance for further studies: first of all, the atheroma growth does not proceed in time with the same velocity, depending on the value of λ and β. We can roughly define two steps: in the first one the turnover between plaque and blood is faster and the evolution of the system is more easily subject to modification (i.e. with pharmacological terapy) as indicated by the behavior of the variance; in the second step the atheroma evolves slowly in time, but a variation of the future destiny of the plaque will become much more difficult, then the whole system tends to reach the minimum value of variance.

A simulation of the phenomenon has been carried out for a case of pure sedimentation (i.e. $\beta \to 0$), in order to study the behavior of the variance, which seems to have particular relevance in order to approach the disease from a pharmacological point of view. Another computer simulation which uses both λ and β parameters is actually under elaboration.

Due to dimension-related problems, the standard deviation has been taken into account: for a process involving only sedimentation, the standard deviation assumes the value:

$$\sigma\{N(t)\} = \sqrt{(m - n)(1 - \exp\{-\lambda t\})\exp\{-\lambda t\}}, \tag{20}$$

and the derivative with respect to time will be:

$$\frac{d\sigma\{N(t)\}}{dt} = \frac{2(m - n)\lambda \exp\{-2\lambda t\} - (m - n)\lambda \exp\{-\lambda t\}}{2\sqrt{(m - n)(1 - \exp\{-\lambda t\})\exp\{-\lambda t\}}} \tag{21}$$

Considering the standard deviation only for $t > 0$, it has been arbitrarily fixed $m - n = 30$, with λ ranging from 0.01 to 50, in order to qualitatively evaluate the process. It was calculated the time t necessary to standard deviation to reach their maximum value for different λ. Some of the results are as follows:

$$\lambda = 0.1 \quad \begin{cases} \sigma_{MAX} \approx 2.73861279 \\ t \approx 6.93144531 \end{cases}$$

$$\lambda = 0.3 \quad \begin{cases} \sigma_{MAX} \approx 2.73861279 \\ t \approx 2.31054688 \end{cases}$$

$$\lambda = 0.5 \quad \begin{cases} \sigma_{MAX} \approx 2.73861279 \\ t \approx 1.38632813 \end{cases}$$

$$\lambda = 0.7 \quad \begin{cases} \sigma_{MAX} \approx 2.73861279 \\ t \approx 0.99023438 \end{cases}$$

$$\lambda = 0.9 \quad \begin{cases} \sigma_{MAX} \approx 2.73861279 \\ t \approx 0.77011719 \end{cases}$$

The results show that λ is the rate determining parameter for the process: performing the same calculus for β the result is the same. The importance of λ and β seem to be in agreement with some clinical and epidemiological observations, like the tendency to stability of the lesion in the old patients, or after a long disease period. The numerical simulation will also be of great importance in order to improve the model, and to suggest other further developments.

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UM MODELO MATEMÁTICO DO FENOMENO DA SEDIMENTAÇÃO E SUSPENSÃO NO DESENVOLVIMENTO DO ATEROMA

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RESUMO – Apresentamos um modelo matematico de simulação do desenvolvimento do ateroma. O modelo toma en consideração a sedimentação possivel bem como os fenômenos de suspensão que verificamse entre a placa ateromatica e o sangue conforme a teoria dos processos estocásticos, em que as interracçoes podem ser estudadas como un caso dum processo Yule-Furry. Indicamos tambem o valor calculado previsto das particulas sedimentadas e a análise de variáncia. Os resultados principais revelam que o crescimento da placa esta grandemente afectado pelos valores da sedimentação e parametros de suspenção, enquanto que a variáncia do fenômeno em su totalidade parece indicar o intervalo de tempo em que uma terapia farmacológica pode ser mais efectiva.

PALAVRAS-CHAVES: Ateroma, Sedimentação e resuspensão, Teoria dõs processos estocásticos.