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# ANISOTROPY IN INFLAMMATORY SYSTEMIC DISEASES – A THEORETICAL MODEL

BY

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**Abstract.** Microbiota refers to the total microorganisms of the microbial community, while the term microbiome refers to a group of microbes that includes bacteria, bacteriophages, fungi, protozoa and viruses. Microbiota is considered to be an organ with its own functions that can modulate the expression of genes involved in the defense of mucosal barrier, angiogenesis and postnatal intestinal maturation. Changes in the composition of gut microbiota, *i.e.* dysbiosis, may be associated with nosocomial infections, necrotizing enterocolitis in premature infants, inflammatory bowel disease (IBD), obesity, rheumatologic autoimmune diseases and allergies. Dysbiosis increases intestinal permeability and the microbial translocation through the mucosa, thus resulting in inflammation and metabolic endotoxemia. Therefore, a large number of proinflammatory cytokines and oxygen free radicals are generated, all of which are considered triggers for the development of immuno-inflammatory systemic diseases. Many clinical studies have examined the link between autoimmune diseases and dysbiosis using 16S rRNA genetic analysis. Clear evidences of association with intestinal dysbiosis have been described in patients diagnosed with IBD, spondylarthropathies, rheumatoid arthritis or systemic lupus erythematosus. A mathematical model based on group invariance is developed.

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## 1. Introduction

Bacterial intestinal flora includes about $10^{14}$ bacteria which represents 10 times more than the number of cells in the human body (Arrieta *et al*., 2014; Saavedra and Dattilo, 2012). Since birth, the normal intestinal microbiota contributes to the development of intestinal function, modulates the immune system, helps to regulate and maintain intestinal function, provides protection against infection and tolerance to food intake. We can talk about a symbiosis of the bacteria-host interaction. Intestinal microbiota diversity includes more than 1,500 microbial species, dominant bacteria group being phyla species: Firmicutes and Bacteroidetes. The phyla group also includes: Proteobacteria, Actinobacteria, Fusobacteria and Verrucomicrobia (Human Microbiome Project C, 2012).

Microbiota has multiple roles in the development of the intestinal immune system by: the modulation of intestinal mucous layer and lymphoid structures, differentiation of immune cells and immune mediators production, positive stimulatory effect on the innate and adaptive immune system (Akira, 2006).

Changes in the composition of gut microbiota - dysbiosis - may be associated with nosocomial infections, necrotizing enterocolitis in premature babies, IBD, obesity, rheumatologic autoimmune diseases and allergies. Dysbiosis increases intestinal permeability and the microbial translocation through the mucosa, thus resulting inflammation and metabolic endotoxemia. Therefore, a large number of proinflammatory cytokines and free radicals are generated (Seksik and Langella, 2008).

Dysbiosis influence the intestinal mucosa by interacting with epithelial cells and by the enteric nervous system, leading to changes in intestinal motility, sensory function and the perception of pain (Konturek, 2011). Also, dysbiosis is associated with the development of gastrointestinal and extraintestinal disorders, as well as with an impaired liver function (Seksik and Langella, 2008; Mondot *et al*., 2013).

## 2. Microbiota and IBD

Genetics and environmental factors and the host immunity forms a triad that it has been shown to regulate the TCR function (Toll like receptor). When this relationship is disturbed, it can develop aberrant TCR signals which contribute to the formation of inflammasomes that will cause intestinal inflammation (IBD) (Frosali *et al*., 2015).

Risk factors for the occurrence of IBD include factors that influence the composition of intestinal microbiota - maternal exposure, breastfeeding, diet, antibiotics, infections and factors affecting mucosal immune system - smoking, NSAIDs, oral contraceptives, vaccination, intestinal permeability, appendectomy, stress (Danese *et al*., 2004). A model of colitis on laboratory mice showed that, after the administration of 4 antibiotics for 4 weeks, the deletion of commensal gut microbiota can cause severe intestinal mucosal impairment (Rakoff-Nahoum *et al*., 2004). Extended use of antibiotics is associated with increased risk of Crohn's disease (CD), but not with ulcerative colitis (UC) (Ungaro *et al*., 2014).

One study attempted to investigate the impact of IBD on intestinal microbiota being analyzed 89 sigmoid mucosal biopsies in healthy individuals and in patients with CD and UC who achieved remission. On these biopsy samples 16sDNA and rARN genetic analysis were performed. Results showed an abundance of Bacteroides in the control group and in patients with UC, an increase of Firmicutes in both IBD, a reduced activity of Faecalibacteria in patients with CD, an increase in the prevalence and activity of Papillibacter in healthy persons; only Prevotella was positively associated with CD (Rehman *et al*., 2015).

Dysbiosis in CD is characterized by: a greater number of mucosal bacteria compared to healthy individuals, alteration of the balance between beneficial and aggressive bacteria and by the reducing of the phyla diversity group Firmicutes and Bacteroides (Sartor, 2011). Increased prevalence of intracellular pathogens in CD may be due to the innate immune system's inability to control persistent infections caused by intracellular bacteria.

Patients with ileal and colonic CD have a low concentration of commensal bacteria concerning the Clostridiales group as Faecalibacterium prausnitzii and Roseburia (Willing *et al*., 2010), these being regarded as predictive marker for postoperative ileal CD (Sokol *et al*., 2008). An increased number of bacterial species found in CD include Escherichia coli especially B2 and D groups and those with adherent / invasive strains associated with a severe ileal disease (Kotlowski *et al*., 2007).

## 3. Microbiota and Inflammatory Rheumatic Diseases

Except reactive arthritis in which there are clear evidences that bacterial infections can cause articular manifestations, currently studies show only hypotheses regarding the role of gut microbiota in immune-mediated arthritis. However, a study conducted on mice having ankylosing spondylitis (AS) and positive antigen HLA-B27 and which were maintained in germ-free conditions highlighted that they didn't developed articular inflammation (Jacques and Elewaut, 2008).

Recent studies argue that, intestinal dysbiosis in patients with SA correlates with the presence of the antigen HLA-B27. To detect bacteria

associated to HLA-B27, 16S rRNA sequencing had been used and elevated populations of Paraprevotella and Bacteroides vulgatus have been highlighted (Lin *et al*., 2014). Altered intestinal bacterial composition characterized by: increasing populations of Lachnospiraceae, Ruminococcaceae, Rikenellaceae, Porphyromonadaceae, Bacteroidaceae, alongside the decreasing of Veillonellaceae and Prevotellaceae constitutes a risk factor for developing SA (Costello *et al*., 2015).

A recently published study supports the important role of intestinal dysbiosis (especially Dialister gender) in spondylarthropathies. There have been included 27 patients of which 14 showed microscopic intestinal inflammation and 13 without gut inflammation. Ileal and colonic biopsies were performed. 16SrARN sequences were used in order to compare the intestinal microbial composition. The results showed that the microbiota of patients with spondylarthropathies was associated with intestinal inflammation and Dialister gender was positively correlated with the ASDAS score (Ankylosing Spondylitis Disease Activity Score) (Tito *et al*., 2016).

Other diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) may have as pathogenic mechanism intestinal dysbiosis which contributes to the development of arthritis through activation of autoreactive T cells in the gut (Maeda *et al*., 2016). Dysbiosis in RA is characterized by a depletion of Haemophilus spp. - negatively correlated with the level of autoantibodies - and an increasing of Lactobacillus salivarius - especially in cases of very high RA activity (Zhang *et al*., 2015). Regarding SLE patients, trials evidenced a significant decrease in Firmicutes and Firmicutes/Bacteroidetes ratio and a significant increase in Clostridiaceae and Lachnospiraceae groups that correlated with disease progression (Hevia *et al*., 2014).

## 4. Microbiota and IBD Associated with Articular Manifestations

Regarding the association between IBD and rheumatic disorders, namely AS, it must not forget that these conditions have common genetic background and are considered distinct phenotypes of an immune-mediated inflammatory disorder. The strongest genetic association is represented by the antigen HLA-B27.

Intestinal epithelial cells produce mucins and antimicrobial peptides such as lysozyme, defensins and lectins that have a critical role in intestinal homeostasis. Patients with active CD show a marked decrease of DEFA5 and DEFA6 α-defensins, leading to an impaired mucosal commensal microbial flora. Controversially, the studies showed an increased expression of α-defensins in patients with SA having also subclinical ileal inflammation (Wehkamp *et al*., 2005).

Regarding IL-17 / IL-22 cytokines relevant to IBD and spondylarthropathies, clear evidences indicate that the interaction between gut

microbiota and host causes the activation of immune cells with subsequent production of these types of proinflammatory cytokines (Shaw *et al*., 2012).

## 5. Mathematical Model

Inflammation results from the accumulation of multiple alterations in a single transformed tissue. Even if the probability of transformation is extremely low for a single tissue, inflammation could arise by chance within a lifetime if many tissue layers are at risk (see the above-mentioned risk factors). Many common inflammations exhibit an increase in incidence with age, which can be described by a simple equation:

$$p = bt^k$$

Parameters are *p* (probability of inflammation), *b* (a constant), *t* (age of individual), and *k* (the number of rate-limiting stages of inflammation). In a particular case, when the inflammation can be associated to cancer, the equation fits the epidemiology of colorectal cancer when *k* is 5 or 6.

This equation does not include many biological parameters, which are presumably incorporated into its constant *b*. Intuitively, inflammation incidence should increase with greater numbers of cells at risk, with greater numbers of cell divisions, and with higher mutation rates.

In this paper we present a simple algebraic equation that relates small biological features (adult stem cells and their niches, tissue size, numbers of rate-limiting driver mutations, and mutation rates) with the epidemiology of inflammatory diseases.

The probability of inflammation is $10^{-36}$ when the mutation rate (*u*) is $10^{-6}$ mutations per gene per division and *k* is six. It is highly improbable that inflammation will arise in a single cell after a single division. A more useful calculation is the probability of inflammation after the many divisions that occur during a human lifetime, and in just one of the many tissues at risk in the body. The approach is based on the trick that the probability of "something" plus the probability of "not something" equals one. The probability of not accumulating a critical mutation (1-*u*) in one cell lineage after a certain number of divisions (*d*) is:

$$p = (1-u)^d$$

With more divisions, the probability of no mutation decreases. It follows that the probability of mutation after d divisions is:

$$p = 1-(1-u)^d$$

For multiple (k) genes:

$$p = [1-(1-u)^d]^k$$

The above equation calculates the probability of a single cell accumulating all k driver mutations after d divisions. We must note that this model was developed in the case of isotropic inflammation.

*In vivo*, biological structures display, by their own nature, an anisotropic behavior. In this context, the following problem arises: can the above results be generalized to the anisotropic case?

In order to solve this problem, let us first make the following substitutions, in accordance with the one-dimensional model we developed:

$$\begin{aligned} &p = [1-(1-u)^d]^k \\ &p = x \\ &[1-(1-u)d]^k = y^2 \end{aligned}$$

It results that the inflammation probability law takes the form:

$$y^2 = x \tag{1}$$

The plane geometry associated to Eq. (1) can be founded on a parametric group which must make the form from relation (1) invariant. This group can be best revealed if the homogenous coordinates $(y, x)$ are used in the form:

$$\frac{x_1}{x} = \frac{x_2}{y} = \frac{x_3}{1} \tag{2}$$

where

$$\begin{aligned} &x = [1-(1-u)^d]^k \\ &y = [1-(1-u)d]^{k/2} \end{aligned} \tag{3}$$

case in which Eq. (1) becomes:

$$x_2^2 - x_1 x_3 = 0 \tag{4}$$

In this situation, the conic from relation (4) accepts the canonic parameterization:

$$\frac{x_1}{t^2} = \frac{x_2}{t} = \frac{x_3}{1} \tag{5}$$

where $t$ is a real parameter, and its invariance group is the three-parameters group generated by the homographic transformation of the $t$ parameter. If this transformation is written under a more convenient form,

$$t = \frac{t + \alpha_1}{1 - \alpha_2 - \alpha_3}, \tag{6}$$

which highlights the unit transformation for $\alpha_1 = \alpha_2 = \alpha_3 = 0$ , then using Eq. (5) the following transformation relations for the parameters $x_1$, $x_2$ result

$$\begin{aligned} x_1 &= \frac{x_1 + 2\alpha_1 x_2 + \alpha_1^2}{\alpha_3^2 x_1 - 2\alpha_3 (1 - \alpha_2) x_2 + (1 - \alpha_2)^2} \\ x_2 &= \frac{-\alpha_3 x_1 + (1 - \alpha_2 - \alpha_1 \alpha_3) x_2 + \alpha_1 (1 - \alpha_2)}{\alpha_3^2 x_1 - 2\alpha_3 (1 - \alpha_2) x_2 + (1 - \alpha_2)^2} \end{aligned} \tag{7}$$

from which a continuous two variables with three parameters group can be observed. The Lie algebra (Duistermaat and Kolk, 2000) is given by the operators:

$$\begin{aligned} L_1 &= 2y \frac{\partial}{\partial x} + \frac{\partial}{\partial y} \\ L_2 &= 2x \frac{\partial}{\partial x} + y \frac{\partial}{\partial y} \\ L_3 &= 2xy \frac{\partial}{\partial x} + \left(2y^2 - x\right) \frac{\partial}{\partial y} \end{aligned} \tag{8}$$

with the commutation relations:

$$\begin{aligned} \left|L_1, L_2\right| &= L_1 \\ \left|L_2, L_3\right| &= L_3 \\ \left|L_3, L_1\right| &= -2L_2 \end{aligned} \tag{9}$$

where inhomogeneous coordinates were taken into account in order to simplify the writing.

As it should be, the conics in relation (4) appear in this situation as the Eq. (8) group's invariant varieties with two parameters, and this is why they are invariant only with regard to the first two operators from relation (8). The issue at hand is not to find the two-parameters invariant varieties families, but to find the three-axial that holds three parameters: the main inflammations, *i.e.* the eigenvalues of the inflammations tensor. Now the inflammations evolution group remains to be solved, which must be isomorphic to the group from Eq. (8). In order to highlight it we must note that the main inflammations are the solution to the secular equation of the respective matrix, which can be written as:

$$y^3 + 3a_1 y^2 + 3a_2 y + a_3 = 0 \tag{10}$$

where $3a_1, 3a_2, a_3$ are the orthogonal invariants of the inflammations matrix. If the inflammation state varies from $y_1, y_2, y_3$ to $y'_1, y'_2, y'_3$ then an algebra theorem (Burnside, 1960) shows that between the secular equations, which have the respective values as roots, a linear relation takes place, generated by the homographic transformation

$$y' = \frac{ay + b}{cy + d} \tag{11}$$

which gives a three-parameters group but in three variables. By writing the roots of the curve from relation (10) in the Barbilian form (Barbilian, 1967; Kelly, 1954),

$$y' = \frac{h + \varepsilon_i \bar{h} k}{1 + \varepsilon_i k} \tag{12}$$

where $\varepsilon_i^3 = 1$, $h, \bar{h}$ are quantities conjugated one to the other, and $k$ is a one-module complex factor, the transformation from Eq. (11) induces upon the quantities $h, \bar{h}, k$ the real transformations

$$\begin{aligned} h' &= \frac{ah + b}{ch + d} \\ \bar{h}' &= \frac{a\bar{h} + b}{c\bar{h} + d} \\ k' &= \frac{c\bar{h} + d}{ch + d} k \end{aligned} \tag{13}$$

which form a three variables with three parameters group (Burnside, 1960), *i.e.* the Barbilian group.

This group is simple transitive, with the infinitesimal generators given by the operators:

$$\begin{aligned} A_1 &= \frac{\partial}{\partial h} + \frac{\partial}{\partial \bar{h}} \\ A_2 &= h \frac{\partial}{\partial h} + \bar{h} \frac{\partial}{\partial \bar{h}} \\ A_3 &= h^2 \frac{\partial}{\partial h} + \bar{h}^2 \frac{\partial}{\partial \bar{h}} + \left(h - \bar{h}\right) k \frac{\partial}{\partial k} \end{aligned} \tag{14}$$

which reveals for the associated Lie algebra a structure that is identical with the one from Eq. (9). Therefore, the two groups are isomorphic, the operators (8) and (14) being generated by the one and the same algebra (4). Moreover, the group (14), being simple transitive, is definitely measurable, its elementary measure being given by the differential three-form:

$$\frac{dh \wedge d\bar{h} \wedge dk}{\left(h-\bar{h}\right)^2 k} \tag{15}$$

As such, in the field variables space $\left(h,\bar{h},k\right)$ a probabilities theory can be apriori constructed using the elementary probability

$$dP = \frac{dh \wedge d\bar{h} \wedge dk}{\left(h-\bar{h}\right)^2 k}$$

As usual, the quadratic root of this function is defined up to an arbitrary unimodular factor, and it can be assimilated to the wave function analogue. Then, it will satisfy a Schrödinger type equation, equation which defines geodesics in a fractal space-time.

The issue now at hand is to find the invariant varieties families of the group (8) with three parameters, having group (14) associated as a parameters group. In our opinion these functions can provide for an answer to the problem of the correlation between the one-dimensional and three-dimensional behaviors of the inflammation.

These varieties families will be solutions of the Stoka (Stoka, 1968) equations:

$$\begin{aligned}
&2y\frac{\partial f}{\partial x}+\frac{\partial f}{\partial y}+\frac{\partial f}{\partial h}+\frac{\partial f}{\partial \bar{h}}=0\\
&2x\frac{\partial f}{\partial x}+y\frac{\partial f}{\partial y}+h\frac{\partial f}{\partial h}+\bar{h}\frac{\partial f}{\partial \bar{h}}=0\\
&2xy\frac{\partial f}{\partial x}+\left(2y^2-x\right)\frac{\partial f}{\partial y}+h^2\frac{\partial f}{\partial h}+\bar{h}^2\frac{\partial f}{\partial \bar{h}}+\left(h-\bar{h}\right)k\frac{\partial f}{\partial k}=0
\end{aligned} \tag{16}$$

This system admits solutions of the form:

$$f\left(\alpha,k_0^2\right)=\text{const.} \tag{17}$$

where:

$$\alpha = \frac{\sqrt{x-y^2}\left(h-\bar{h}\right)}{x-\left(h-\bar{h}\right)y+h\bar{h}}$$
$$k_0^2 = k^2\,\frac{x-2y\bar{h}+\bar{h}^2}{x-2yh+h^2} \tag{18}$$

It can be observed that the last of these integrals is a one-module complex one. In principle, $f$ can be any function which is continuous and derivable in its variables. It is not yet known what kind of interpretation can a general solution such as Eq. (17) have, but some specific integrals values from relation (18) can still be interpreted. Thus, if the one-dimensional inflammation is monotonous, then Eq. (18) must fulfill the condition $y^2 = x$, fact which leads to the specific value $x = 0$. In this case, the second relation (18) gives:

$$k_0 = k\,\frac{y-\bar{h}}{y-h} \tag{19}$$

from which we can write $y$ as:

$$y = \frac{\bar{h}k - hk_0}{k-k_0} \tag{20}$$

The result we obtained in this case is important mainly because it shows that $y$ can be identified in a specific case with one of the main inflammations. Indeed, if $k_0 \equiv (-1, -\varepsilon, -\varepsilon^2)$ then the situation from Eq. (12) is again reached. Therefore, we can state that in both these specific cases the inflammation in the one-dimensional case can be considered as one of the internal inflammations eigenvalues. However, we can draw more from Eq. (20). If this equation is written for $k_0 = -1$,

$$y = \frac{h+\bar{h}k}{1+k} \tag{21}$$

and $h, \bar{h}, k$ are explicitly written with regard to the main inflammation, and also the system of Eqs. (12) is solved with regard to $h, \bar{h}, k$, then the following relations can be found:

$$h = -\frac{y_2y_3 + \varepsilon y_3y_1 + \varepsilon^2 y_1y_2}{y_1 + \varepsilon y_2 + \varepsilon^2 y_3}$$
$$k = \frac{y_1 + \varepsilon^2 y_2 + \varepsilon y_3}{y_1 + \varepsilon y_2 + \varepsilon^2 y_3} \tag{22}$$

These can be related with the above-mentioned parameters by:

$$k = -e^{3i\xi}$$
$$h = \lambda + \frac{\mu}{\sqrt{3}}\left(\sin 3\xi - i\cos 3\xi\right) \tag{23}$$

where

$$\tan\xi = \frac{2y_1 - y_2 - y_3}{\sqrt{3}\left(y_2 - y_3\right)}$$
$$\lambda = \frac{1}{3}\left(y_1 + y_2 + y_3\right) \tag{24}$$
$$\mu = \frac{1}{\sqrt{2}}\left\{\sum\left(y_2 - y_3\right)^2\right\}^{\frac{1}{2}}$$

The quantity from Eq. (24) is the known Lode-Nadai parameter of the tensions tensor.

If we use Eq. (23) in relation (21), we obtain the following:

$$y = \lambda + \mu\sin\xi \tag{25}$$

relation which, in the case of the absence of anisotropic inflammation, is reduced to:

$$y = \mu\sin\xi \tag{26}$$

From this it results that the one-dimensional inflammation can be identified with the quantity $\mu$ from Eq. (24) only if the inflammations which are orthogonal to the direction of disease expansion are very close to each other. Indeed, in this case, from relation (24) it results that $\tan\xi \to \infty$, and, thus, $\sin\xi \to 1$.

## 6. Conclusions

The main conclusions of the present paper are presented in the following:

i) The gut microbiota plays an important role in the development of immuno-inflammatory diseases, namely in intestinal and articular disorders. Nevertheless, the specifically pathogenic mechanism remain a challenge for the practitioner physician. The analysis of gut microbiota opens new perspectives in research and for understanding of these systemic diseases.

ii) Starting from an isotropic model, an anisotropic theoretical model is developed for inflammatory disease evolution.

We note that the same model can also be applied, because of its theoretical implications, in engineering and materials science, in various domains, such as the ones described in (Agape *et al*., 2016; Agape *et al*., 2017; Gaiginschi *et al*., 2011; Gaiginschi *et al*., 2014a; Gaiginschi *et al*., 2014b; Gaiginschi *et al*., 2017; Vornicu *et al*., 2017).

## REFERENCES


Agape I., Gaiginschi L., Gaiginschi R., Baltagiu D., *Upon a Simple Method for Generating Transversal Profile of the Volumic Blower Rotor Used in Supercharging ICE*, Ingineria Automobilului, **38**, 22-25 (2016).

Agape I., Gaiginschi L., Ianuş G., Cimpoeşu N., *The Analysis of an Internal Combustion Engine Breakdown - Case Study*, IOP Conference Series: Materials Science and Engineering, **209**, *1*, 012077 (2017).

Akira S., Uematsu S., Takeuchi O., *Pathogen Recognition and Innate Immunity*, Cell, 124, 783-801 (2006).

Arrieta M.C., Stiemsma L.T., Amenyogbe N., Brown E.M., Finlay B., *The Intestinal Microbiome in Early Life: Health and Disease*, Front Immunol., **5**, 427 (2014).

Barbilian D., *Mathematical Works*, Didactics and Pedagogy Publishing House, Bucharest (1967).

Burnside W.S., *The Theory of Equations*, Constable, Dover (1960).

Costello M.E., Ciccia F., Willner D., Warrington N., Robinson P.C., Gardiner B., Marshall M., Kenna T.J., Triolo G., Brown M.A., *Intestinal Dysbiosis in Ankylosing Spondylitis*, Arthritis Rheumatol, **67**, 686-691 (2015).

Danese S., Sans M., Fiocchi C., *Inflammatory Bowel Disease: The Role of Environmental Factors*, Autoimmunity Reviews, **3**, *5*, 394-400 (2004).

Duistermaat J.J., Kolk J.A.C., *Lie Groups*, Springer-Verlag, Berlin (2000).

Frosali S., Pagliari D., Gambassi G., Landolfi R., Pandolfi F., Cianci R., *How the Intricate Interaction Among Toll-Like Receptors, Microbiota, and Intestinal Immunity Can Influence Gastrointestinal Pathology*, J. Immunol. Res., 489821 (2015).

Gaiginschi L., Gaiginschi R., Agape I., Hantoiu V., *Researches Regarding Impact Energy Dissipation by Breaking for Front – Rear Collisions*, Ingineria Automobilului, **18**, 20-23 (2011).

Gaiginschi L., Agape I., Sachelarie A., Girbaci M.A., *Virtual High Speed Diesel Engine–A Simulated Experiment. Part I: Combustion Dynamics*, Applied Mechanics and Materials, **659**, 189-194 (2014a).

Gaiginschi L., Agape I., Sachelarie A., Girbaci M.-A., *Virtual High Speed Diesel Engine – A Simulated Experiment. Part II:The Influence of Polytropic Exponent upon Combustion Product Formation*, Applied Mechanics and Materials, **659**, 195-200 (2014b).

Gaiginschi L., Agape I., Talif S., *Upon the Reconstruction of Accidents Triggered by Tire Explosion. Analytical Model and Case Study*, IOP Conf. Series: Materials Science and Engineering, **252**, 012016 doi:10.1088/1757-899X/252/1/012016 (2017).

Hevia A., Milani C., López P., Cuervo A., Arboleya S., Duranti S., Turroni F., González S., Suárez A., Gueimonde M., Ventura M., Sánchez B., Margolles A., *Intestinal Dysbiosis Associated with Systemic Lupus Erythematosus*, MBio, **5**, e01548-14 (2014).

Human Microbiome Project C, *Structure, Function and Diversity of the Healthy Human Microbiome*, Nature, **486**, 207-214 (2012).

Jacques P., Elewaut D., *Joint Expedition: Linking Gut Inflammation to Arthritis*, Mucosal Immunology, **1**, *5*, 364-371 (2008).

Kelly P.J., *Barbilian Geometry and the Poincaré Model*, American Mathematical Monthly, **61**, 311-319 (1954).

Kotlowski R., Bernstein C.N., Sepehri S., Krause D.O., *High Prevalence of Escherichia Coli Belonging to the B2+D Phylogenetic Group in Inflammatory Bowel Disease*, Gut, **56**, *5*, 669-675 (2007).

Konturek P.C., Brzozowski T., Konturek S.J., *Stress and the Gut: Pathophysiology, Clinical Consequences, Diagnostic Approach and Treatment Options*, J. Physiol. Pharmacol., **62**, 591-599 (2011).

Lin P., Bach M., Asquith M., Lee A.Y., Akileswaran L., Stauffer P. *et al*., *HLA-B27 and Human Beta2-Microglobulin Affect the Gut Microbiota of Transgenic Rats*, PLoS One, 9, e105684 (2014).

Maeda Y., Kurakawa T., Umemoto E., Motooka D., Ito Y., Gotoh K., Hirota K., Matsushita M., Furuta Y., Narazaki M., Sakaguchi N., Kayama H., Nakamura S., Iida T., Saeki Y., Kumanogoh A., Sakaguchi S., Takeda K., *Dysbiosis Contributes to Arthritis Development via Activation of Autoreactive T Cells in the Intestine*, Arthritis Rheumatol., doi: 10.1002/art.39783 (2016).

Mondot S., de Wouters T., Dore J., Lepage P., *The Human Gut Microbiome and its Dysfunctions*, Dig. Dis., **31**, 278-285 (2013).

Rakoff-Nahoum S., Paglino J., Eslami-Varzaneh F., Edberg S., Medzhitov R., *Recognition of Commensal Microflora by Toll-Like Receptors is Required for Intestinal Homeostasis*, Cell, **118**, 229-241 (2004).

Rehman A., Raush P., Wang J., Skieceviciene J., Kiudelis G., Bhagalia K., Amarapurkar D., Kupcinskas L., Schjreiber S., Rosenstiel P., Baines J.F., Ott S., *Geographical Patterns of the Standing and Active Human Gut Microbiome in Health and IBD*, Gut, **0**, 1-11 (2015).

Saavedra J.M., Dattilo A.M., *Early Development of Intestinal Microbiota: Implications for Future Health*, Gastroenterol Clin North Am., **41**, 717-731 (2012).

Sartor R.B., *Key Questions to Guide a Better Understanding of Host-Commensal Microbiota Interactions in Intestinal Inflammation*, Mucosal Immunology, **4**, *2*, 127-132 (2011).

Seksik P., Langella P., *Faecalibacterium Prausnitzii is an Anti-Inflammatory Commensal Bacterium Identified by Gut Microbiota Analysis of Crohn Disease Patients*, Proceedings of the National Academy of Sciences of the United States of America, **105**, *43*, 16731-16736 (2008).

Shaw M.H., Kamada N., Kim Y.G., Nunez G., *Microbiota-Induced IL-1Beta, but not IL-6, is Critical for the Development of Steady-State TH17 Cells in the Intestine*. J. Exp. Med., **209**, 251-258 (2012).

Sokol H., Pigneur B., Watterlot L., Lakhdari O., Bermúdez-Humarán L.G., Gratadoux J.J., Blugeon S., Bridonneau C., Furet J.P., Corthier G., Grangette C., Vasquez N.,

Pochart P., Trugnan G., Thomas G., Blottière H.M., Doré J., Marteau P., Szabo G., *Gut-Liver Axis in Alcoholic Liver Disease*, Gastroenterology, **148**, 30-36 (2015).

Stoka M.I., *Geometrie Integrale, Memorial des Sciences Mathematiques*, **165**, Gauthier-Villars, Paris (1968).

Tito R.Y., Cypers H., Joossens M., Varkas G., Van Praet L., Glorieus E., Van den Bosch F., De Vos M., Raes J., Elewaut D., et al., *Dialister as Microbial Marker of Disease Activity in Spondyloarthritis*, Arthritis Rheumatol., doi: 10.1002/art.39802 (2016).

Ungaro R., Bernstein C.N., Gearry R., Hviid A., Kolho K.L., Kronman M.P., Shaw S., Van Kruiningen H., Colombel J.F., Atreja A., *Antibiotics Associated with Increased Risk of New-Onset Crohn's Disease but not Ulcerative Colitis: A Meta-Analysis*, Am. J. Gastroenterol., **109**, 1728-1738 (2014).

Vornicu V., Ulian T., Rakosi E., Manolache Gh., Gaiginschi L., *Theoretical Model for Determination of the Spark Ignition Engine Thermo-Gasodynamic Parameters on Various Functional Conditions*, IOP Conference Series: Materials Science and Engineering, **252,** *1*, 012073 doi:10.1088/1757-899X/252/1/012073 (2017).

Wehkamp J., Salzman N.H., Porter E., Nuding S., Weichenthal M., Petras R.E., Shen B., Schaeffeler E., Schwab M., Linzmeier R., Feathers R.W., Chu H., Lima H. Jr., Fellermann K., Ganz T., Stange E.F., Bevins C.L., *Reduced Paneth Cell α-Defensins in Ileal Crohn's Disease*, Proc. Natl. Acad. Sci. USA, **102**, 18129-18134 (2005).

Willing B.P., Dicksved J., Halfvarson J., Andersson A.F., Lucio M., Zheng Z., Jarnerot G., Tysk C., Jansson J.K., Engstrand L., *A Pyrosequencing Study in Twins Shows that Gastrointestinal Microbial Profiles Vary with Inflammatory Bowel Disease Phenotypes*, Gastroenterology, **139**, *6*, 1844-1854 (2010).

Zhang X., Zhang D., Jia H., Feng Q., Wang D., Liang D., Wu X., Li J., Tang L., Li Y. *et al*., *The Oral and Gut Microbiomes are Perturbed in Rheumatoid Arthritis and Partly Normalized After Treatment*, Nat. Med., **21**, *8*, 895-905 (2015).

## ANIZOTROPIA ÎN BOLILE INFLAMATORII SISTEMICE – UN MODEL TEORETIC

(Rezumat)

Microbiota este considerată un organ cu funcții specifice, ce poate modula expresia genelor implicate în protejarea barierei mucoase, angiogeneză sau maturarea intestinală postnatală. Modificări ale compoziției microbiotei intestinale, numite într-un cuvând disbioză, pot fi asociate cu infecțiile nosocomiale, boala intestinală inflamatorie, obezitate, alergii etc. Disbioza mărește permeabilitatea instestinală și crește rata de mișcare microbiană la nivelul mucoasei, având ca rezultat endotoxemie inflamatorie și metabolică. Toate aceste cauze pot genera boli imuno-inflamatorii sistemice. Plecând de la aceste premise, în prezenta lucrare se construiește un model matematic bazat pe invarianță grupală, care permite extensia de la multiplicarea omogenă și izotropă la cea neomogenă și anizotropă, în cazul evoluției bolilor inflamatorii, cum de regulă se întâmplă în structurile biologice.