STOCHASTIC CANALIZATION OF PHENOTYPIC DEFORMATIONS DURING ONTOGENESIS

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Abstract: This article presents a new application of the Stochastic Theory of Volterra-Hamilton Systems of Finsler class to growth and ontogeny and particularly to the study of noise effects on the deterministic model equations for interaction of muscle and adipose tissue in mammals introduced in our previous study. Both normal development and its phenotypic deformation, due to non-optimal nutrition or disease, are considered. Efficient energy (ATP) usage by the system as a whole is centrally important. Feynman-Kac solutions to the noisy perturbation equations and sojourn time probabilities for the Sasaki lift Riemannian diffusion are obtained, based on the Riemannian Embedding Theorem for Finslerian Diffusion. Stochastic canalization of development, after C. H. Waddington, is proved for this mathematical model.

AMS Subject Classification: 92C30, 53A20, 47D07, 35K40

Key Words: modular mechanics, Markov diffusions, Finsler geometry, physiology

1. Introduction and Preliminaries

The mathematical analysis of the adipose/muscle system in development is here

Received: June 24, 2016

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further studied, based on previous work, [2]. We found structures from Finsler geometry naturally occurring because of the biologically significant role of the “fat to lean” ratio, F/L , found experimentally, [21], [22], [18], [15]. Such ratios are at the heart of Finsler geometry, [1], [6], [7], [8], [9]. The general set up is the following second order system of ordinary differential equations, or SODE’s for short: Letting (X^i, N^i) , $i \in \{1, \dots, n\}$, denote the natural phase-space coordinates in an open region of the tangent bundle TM consider the SODE system

$$\begin{cases} \frac{dX^i}{dt} = k_i N^i + f^i \quad (\text{not summed}) \\ \frac{dN^i}{dt} = -G_{jk}^i N^j N^k + r_j^i N^j + e^i \quad (\text{summed on repeated indices}) \end{cases}, \quad (1)$$

where all coefficients (possibly) depend on X^i , N^i , t and the n^3 functions G_{jk}^i are smooth on TM and homogeneous with respect to N^i . The X^i are Volterra production variables whose constant per capita rate of increase is k_i , while the second part of the system, often called population equations, describes how different types of populations $N^i \geq 0$, *grow*(r_j^i), *interact*, (G_{jk}^i), and react to, (e^i) and (f^i), due to environment. For the present modelling purpose there is a population of muscle cells, N^1 , and that of adipose cells, N^2 , with muscle producing IL-6, x^1 , and adipose tissue producing adiponectin, x^2 . The G ’s are constants and the growth rate matrix is $\lambda \delta_j^i$, just a positive constant times the identity matrix. The paper [2], gives a full account of the development of the deterministic model, [11], [13].

Motivation for Finsler. It is the F/L ratio dependence feature that distinguishes the geometry of Finsler from the more familiar Riemannian geometries used in physics or engineering. We now present an informative illustration of its utility by giving a Finslerian description of the rate of total joint production, ds/dt , for(log of) adiponectin, x^2 , and for(log of) IL-6, x^1 . Let us proceed step by step. As a first thought, consider the Root Mean Square (RMS) of the two rates, dx^1/dt , and, dx^2/dt

$$\frac{ds}{dt} = \sqrt{\left[\left(\frac{dx^1}{dt}\right)^2 + \left(\frac{dx^2}{dt}\right)^2\right]} = \sqrt{2} \text{ RMS} = F\left(x, \frac{dx}{dt}\right). \quad (2)$$

This yields the Huxley/Needham Allometric law, a mathematical model of a Bauplan for Ontogenesis, [22], [17], [9], [14], [1], [4], [5]. This law is a consequence of (ATP) energy, (2), being minimized, [1], [10], [12]. However, a more complicated F is needed to capture the role of the F/L ratio,

$$\frac{dx^2}{dx^1} = \frac{y^2}{y^1} = \frac{N^2}{N^1}.$$

We choose instead of (2), a weighted form of the *RMS*,

$$(ds)^2 = g_{ij}(x, y) dx^i dx^j = F^2(x, y). \quad (3)$$

As it is usually expedient to try to keep things as simple as possible, we set, $g_{12} = g_{21} = 0$, in a neighborhood around a fixed point in the production phase space, TM. In other words, the diagonal matrix in (2) now has entries depending on x and y , in an open region of TM. Unfortunately, the “Antonelli’s lemma”, dictates that the g_{ij} has no y -dependence, [1]. We have failed to get F/L ratio dependence in our model of joint production.

Proof of Lemma. A basic property of any Finsler functional, $\frac{ds}{dt} = F\left(x, \frac{dx}{dt}\right)$ is that when the rate vector, $\frac{dx}{dt} = y = (y^1, y^2) = \left(\frac{dx^1}{dt}, \frac{dx^2}{dt}\right)$ (4)

is doubled (or tripled, etc), then the value of F is doubled (or tripled, etc.), as well. This is technically stated: F is positively homogeneous of degree one in y . A direct consequence of this property is that the metric g -tensor in (3) must be positively homogeneous of degree zero. This is another way of saying g_{ij} is actually a function of, x ’s and y^2/y^1 , not simply x ’s and y ’s. This follows from Euler’s theorem on homogeneous functions, [3]. That is, by definition one has

$$g_{12} = g_{21} = \frac{1}{2} \dot{\partial}_1 \dot{\partial}_2 F^2, \quad (5)$$

so that differentiation by y^2 followed by another with respect to y^1 , converts F^2 , a smooth function positively homogeneous of degree 2 in y , into one of degree zero relative to y . Euler’s theorem comes in again when we note that Cartan’s torsion tensor,

$$C_{ijk} = \frac{1}{2} \dot{\partial}_k g_{ij}, \quad (6)$$

holds so that,

$$C_{ijk} y^k = 0. \quad (7)$$

The condition that $g_{12} = 0$ in a region can now be used to obtain the vanishing of Cartan’s torsion which means there is no y -dependence at all and completes the proof.

Therefore, the above motivational arguments show we must have g_{12} non-vanishing for our choice of, ds/dt , in order to secure a model which involves the F/L ratio.

Let us now consider $F(x, y)$ and the metric tensor g_{ij} from [2], our first paper:

$$F^2(x, y) = (y^1)^2 \exp\{2z + 2Q(x)\} \quad (8)$$

$$z = \frac{y^2}{y^1} \quad \text{with} \quad Q(x) = \frac{1}{\tau^2} \left[\frac{x^2}{x^1} + (\tau^2 + 1) \ln(x^1) - \tau^3 \beta_2 x^1 \right],$$

$$g_{11} = (1 - 2z + 2z^2) \exp\{2z + 2Q(x)\} = \frac{1}{2} \dot{\partial}_1 \dot{\partial}_1 F^2$$

$$g_{12} = g_{21} = (1 - 2z) \exp\{2z + 2Q(x)\} = \frac{1}{2} \dot{\partial}_1 \dot{\partial}_2 F^2$$

$$g_{22} = 2 \exp\{2z + 2Q(x)\} = \frac{1}{2} \dot{\partial}_2 \dot{\partial}_2 F^2.$$

[Here, we have removed the $\sim$ symbol over x 's and y 's from the notation of our first paper] and here exhibit a coordinate transformation on allometric production space which converts these x 's into the old coordinates, now written with subscript 0, via

$$x_0^1 = \frac{1}{\beta_1} \ln\{\beta_1 x^1\} \quad x_0^2 = \frac{1}{\beta_2} \ln\{\beta_2 x^2\},$$

and F , as in [2]. The old coordinate expression is now

$$F^2 = (y_0^1)^2 \exp \left\{ 2 \left(\frac{y_0^2}{y_0^1} \right) \exp\{-\beta_1 x_0^1 + \beta_2 x_0^2\} + 2Q(x_0^1, x_0^2) \right\}, \quad (9)$$

$$Q(x_0^1, x_0^2) = \beta_2 \left(\tau + \frac{1}{\tau} \right) x_0^1, \quad \beta_1 = \tau \beta_2.$$

This old form of F is inconvenient for calculations. Instead, we use (8). The condition, $R = 0$, is necessary for phenotypic deformation to be global. Also, the $F(x_0, y_0)$ energy minimizing solutions are of form (1) and are geometrical straight lines so that the allometric law holds.

Using (8) and our result, that $R = -W \exp \left\{ -2 \left(\frac{y^2}{y^1} + Q(x) \right) \right\}$, with constant, $h > V(x) > 0$,

$$W = -\frac{1}{2} [(h - V(x))V_{22} + (V_2)^2]/(h - V(x))^2,$$

with $V(x) = h - \exp\{2Q(x)\}$, so that for Q as in (8),

$$W = Q_{22} = 0,$$

where the notation is that subscript “2” means partial derivative with respect to, x^2 , is taken we arrive at the following theorem.

Theorem 1. *Adding to $Q(x)$ in (8), according to*

$$\widetilde{Q}(x) = Q(x) + 2 \left[\frac{\gamma_1}{\beta_1} \ln(x^1) + \frac{\gamma_2}{\beta_2} \ln(x^2) \right],$$

leads to

$$R = 2 \frac{\gamma_2}{\beta_2} \left(\frac{1}{x^2} \right)^2 \exp \left\{ -2 \left(\frac{y^2}{y^1} + \widetilde{Q}(x) \right) \right\}.$$

So $R < 0$, if and only if, $\gamma_2 < 0$. If $\gamma_2 = 0$, then $R = 0$.

Proof. Note that in this case

$$W = \widetilde{Q}_{22} = -2 \frac{\gamma_2}{\beta_2} \left(\frac{1}{x^2} \right)^2.$$

Thus, we see from this theorem that R is positive (so the geodesic system is stable) because γ_2 is positive. In any case, the coefficients in (9) are no longer constant, even approximately. Also, the change from Q to $\widetilde{Q}$ is linear in the original system of coordinates. $\square$

There are lots of examples of straight line geodesics with, $R \neq 0$. Those systems with R strictly positive have the property: Given a geodesic, γ , and small $\epsilon > 0$, there is a $\delta > 0$ such that any other geodesic curve, φ , will remain within distance ϵ for all time, if the angle between their initial tangent vectors is less than δ . Such a deterministic system is termed, Jacobi Stable. Clearly, (8) is not J-stable in this sense because, $R = 0$. The dynamical equations for (8) are

$$\begin{cases} \frac{d^2 x^1}{dS^2} + \left(\tau + \frac{1}{\tau} \right) \left(\frac{dx^1}{dS} \right)^2 = 0, \\ \frac{d^2 x^2}{dS^2} - \left(\frac{dx^1}{dS} \right)^2 + \left(\frac{dx^2}{dS} \right)^2 + \frac{2}{\tau} \left(\frac{dx^1}{dS} \right) \left(\frac{dx^2}{dS} \right) = 0, \\ dS = \beta_2 \exp\{\lambda t\} dt. \end{cases} \quad (10)$$

Here, S is the total production parameter as used in [1], [2], [3], [4], [5]. The parameter, $\tau = N_*^2/N_*^1$, is the ratio of the adipose to muscle tissue cell populations, at adult size. The positive coefficient β_2 is the interaction intensity. This system arose as a result of an ecological style assumption of commensalism to the effect that muscle tissue provides a place for adipose tissue to reside without the muscle population suffering any ill effects.

It is important to determine possible evolutionary mechanisms for the acquisition of biological robustness for the normal and deformed (adipose/ muscle) cell interactions. This is possible in the present deterministic model, if the system dynamics evolves into one with R , strictly positive. A heterochronic transformation, i.e., time-sequencing change coordinated along production trajectories, is a mechanism for this evolution, [3], [7], [8], [17]. We will use it below.

2. Stochastic Finsler Geometry

Random perturbations of Volterra-Hamilton Systems have focused on diffusions, [3], [7], [8]. Of special interest are the relations between noise and Finslerian curvature discovered some years ago, [3]. For example, in the Berwald class of Finsler geometries, curvature scalar, R , appears explicitly in the Feynman-Kac solutions to the Cauchy initial-boundary value problems of the forward Kolmogorov equations, as in (23), below. Furthermore, we introduce below the so-called sojourn probability, well-known for Riemannian diffusions, and extend this to include Finslerian diffusions, as well, by use of the Finslerian Embedding Theorem.

The main question: How probable is it that a noisy trajectory remains close to its deterministic associate over a fixed interval of time, $[0, T]$. This topic concerned us in previous studies of C.H. Waddington's canalization of embryonic development, [13], [16], [17], [19], [22]. We will see in Section 3, how both the curvature, R , and the divergence of the Cartan torsion, C , play significant roles in the stochastic version of canalization.

One previously found fact about our deterministic model of IL-6 versus adiponectin ($R = 0$) is that normal ontogenic development is dominated by adiponectin with only a modest contribution from hormone IL-6. In fact, J-stability can be induced by a heterochronic change to a positive, R , in a scenario that increased fat production costs more [17], [22]. On the other hand, if the muscle/adipose system becomes more efficient and consequently costs less, then R will be negative and joint production exhibits stochastic canalization. In

either case, this time-sequencing change is largely dependent on adiponectin rather than IL-6, alone. Our calculations show that in the case of the deformed model, only when the two hormones act in conjunction via a positive product, cx^1x^2 added to $\ln(F)$, does J-stability ensue for the deterministic model. Let us now be more precise about Finslerian stochastics.

We will be concerned with a Volterra-Hamilton System from our first paper, [2]. After some parameter change, the system has the general form of (16). Consider smooth solution $x(S) = (x^1(S), \dots, x^n(S))$, $y(S) = (y^1(S), \dots, y^n(S))$ of this SODE (second order differential equation system) with smooth initial conditions,

$$\begin{cases} \frac{dx^i}{dS} = y^i, \\ \frac{dy^i}{dS} = -G_{jk}^i(x, y)y^jy^k, \\ e^i = f^i = 0, \end{cases} \quad (11)$$

$i, j, k \in \{1, 2, \dots, n\}$, using the summation convention on repeated indices (for example each of the second set in (11) has n^2 terms, $n \geq 2$). Here, (x, y) are the natural phase space(local) coordinates in the tangent bundle TM , where M denotes the allometric production space. The equations (11) are Euler-Lagrange equations for the simplest regular problem in the calculus of variations for energy functional, F^2 . Furthermore, $dS = F(x, dx)$ defines the length of any smooth curve $\gamma(t)$ in M by integrating $F(x, dx)$ along $\gamma(t)$. In most applications, S is interpreted as total production or size, [1], [2], [3], [4], [5]. The parameter S in (10) is just another convenient representation of the total production, which we now employ.

Everyone is familiar with the standard mutually orthogonal directions: the tangent, normal and binormal vectors used for navigation by airplane pilots and astronauts. Using similar technique called rolling (see, [6], [8]) a solution of (11) is lifted from TM to the orthonormal frame bundle OM and simultaneously rolled onto a curve in $\mathbb{R}^{2n} = \mathbb{R}^n \times \mathbb{R}^n$, to obtain a smooth curve, $y(S) =$

$(\mu(S), \nu(S))$ in $\mathbb{R}^{2n}$ defined by the $3n$ differential equations

$$\begin{cases} \frac{dx^i}{dS} = y^i + z_j^i \frac{d\mu^j}{dS}, \\ \frac{\delta y^i}{dS} = z_j^i \frac{d\nu^j}{dS}, \\ \frac{dz_j^i}{dS} = -G_{kl}^i(x, y) z_j^l(S) \frac{dx^k}{dS} - C_{kl}^i(x, y) z_j^l(S) \frac{\delta y^k}{dS}, \end{cases} \quad (12)$$

where

$$\frac{\delta y^i}{dS} = \frac{dy^i}{dS} + G_{jl}^i(x, y) y^l \frac{dx^j}{dS}, \quad (13)$$

and the n^3 components G_{jk}^i , are smooth functions of x and y defined on TM and homogeneous of degree zero in y and called the coefficients of the Berwald connection for the SODE in (11). The tensor, C_{jk}^i , is the Cartan torsion with purely covariant form as in (6),

$$C_{lkj} = g_{li} C_{kj}^i = \frac{1}{4} \dot{\partial}_i \dot{\partial}_k \dot{\partial}_j F^2(x, y), \quad (14)$$

using the energy functional $F(x, y)$ (dot indicates partial differentiation with respect to the lower-index-denoted component of y). The noise perturbed equations read (using the same notation as in the deterministic case above, except for the asterisk) as follows:

$$\begin{cases} dx^i = y^i dS + z_j^i * d\mu^j, \\ \delta y^i = z_j^i(S) * dw^j, \\ dz_j^i = -G_{kl}^i(x, y) z_j^l(S) * dx^k - C_{kl}^i(x, y) z_j^l(S) * \delta y^k, \end{cases} \quad (15)$$

where

$$\delta y^i = dy^i + G_{jk}^i(x, y) y^k * dx^j, \quad (16)$$

and the asterisk indicates the use of Stratonovich calculus, [AZ]. The stochastic process $(x(S), y(S), z(S))$ given by (15), (16), lives in the orthonormal frame bundle, OM , where, $z(S) = \{z_j^i(S)\}$, is the orthonormal frame process based on the given norm of (M, F) . A frame is a set of n contravariant (i.e., upper index i) vectors indexed by the n integer values of subscript, j . This $z(S)$ random process projects down onto the tangent bundle TM , with local coordinates

(x^i, y^i) . It is the projected stochastic process that takes the form of a time-homogeneous strong Markov diffusion whose generator is the parabolic partial differential operator

$$D = \frac{1}{2}g^{ij}(\delta_i\delta_j - G_{ij}^k\delta_k) + \frac{1}{2}g^{ij}(\dot{\partial}_i\dot{\partial}_j - C_{ij}^k\dot{\partial}_k) + y^j\delta_j. \quad (17)$$

Also,

$$\delta_i = \partial_i - G_{ik}^r y^k \dot{\delta}_r \quad (18)$$

is a basic vector field, which together with the other basic field, $\dot{\partial}_i$ form the Berwald Basis used to express any vector field, $B(x, y)$, as a linear combination, viz.,

$$B(x, y) = B^h(x, y)\delta_h + B^v(x, y)\dot{\partial}_v, \quad (19)$$

is decomposed uniquely into a horizontal, B^h , and a vertical, B^v , component. The covariant tensor, g^{il} , is the inverse tensor of $g_{ip} = \frac{1}{2}\dot{\partial}_i\dot{\partial}_p F^2$ meaning $g^{il}g_{ip} = \delta_p^l$, is the n by n identity matrix tensor.

When written out completely, D has $2n^2 + n$ terms and the diffusion processes are at least 4 dimensional and is generated by, D . If $y = 0$, $D = D_0$, is the optimal random process (directionally unbiased) in Finsler space. It is unbiased relative to intrinsic directional properties of Finsler geometry, but this is not Riemannian diffusion. The two types can be made compatible because it is possible to embed, D_0 , into Riemannian diffusion theory by use of the Embedding Theorem for Finslerian Diffusions, [6], [8]. Most importantly, there will always be additional drift fields in this embedded Riemannian diffusion, one horizontal and one vertical. This embedding requires a new phase space which is (TM, G) . The G denotes the Sasaki-lift Riemannian metric $G = g \oplus g$ on TM , [6], [8]. Using the Berwald Basis $\{\delta_i, \dot{\partial}_j\}$, the Sasaki metric is a $2n$ by $2n$ block diagonal matrix with g_{ij} for each block. However, this Riemannian diffusion is not optimally random and so is not Brownian motion on (TM, G) , whose generator is Δ_G . The (vertical) drift field for Berwald diffusions as given by components

$$C^v = -\frac{1}{2}g^{vk}C_{kj}^j, \quad (20)$$

which vanish, if and only if, the production geometry is Riemannian. However, the horizontal drift field vanishes for all Berwald geometries, [3],[6]. Yet, when y does not vanish there is still the (horizontal) drift, $y^h\delta_h$, so finally, making use of the fundamental Embedding Theorem, we arrive at the following theorem.

Theorem 2. *The full Riemannian description of the Finslerian diffusion generator is the Sasaki-lift Riemannian diffusion with drift:*

$$\begin{cases} D &= \frac{1}{2}\Delta_G + B, \\ B &= y^h \delta_h + C^v \dot{\partial}_v. \end{cases} \quad (21)$$

Following [6], we denote by $\rho(S, x, y)$ the probability density of the process starting at production size, S_0 , in state x_0, y_0 with generator (17), stopped at the first hitting time to the surface, $y^1 y^2 = 0$, to be in a region $A \subset TM \cap \{y^1 > 0, y^2 > 0\}$ relative to the measure $\sqrt{\det G} \, dx \, dy$ on TM , that is,

$$\mathbb{P}\{(x(S), y(S)) \in A\} = \int_A \rho(S, x, y) \sqrt{\det G} \, dx \, dy.$$

Here, ρ satisfies the forward initial boundary value problem

$$\begin{cases} D^* \rho = \frac{\partial \rho}{\partial S} \\ \lim_{S \searrow 0} \rho(S, x, y) = \rho_0(x, y) \\ \rho \text{ vanishes on, } y^1 y^2 = 0 \end{cases} \quad (22)$$

and ρ is non-zero only on $TM \cap \{y^1 > 0, y^2 > 0\}$ and D^* denotes the adjoint operator relative to the measure $\sqrt{\det G} \, dx \, dy$. The adjoint is computed to be

$$D^* \rho = D\rho - 2y^h \delta_h \rho - 4g^{ih} Q_i \delta_h \rho + g^{iv} C_{ik}^k (\dot{\partial}_v \rho) + V\rho, \quad (23)$$

$V = 2R + 2Im^i l^j Q_{ij} - 2[I^2 m^i m^j 2Im^i l^j - 4g^{ij}] Q_i Q_j + 4y^i Q_i - I^2/2F^2$, with m^i and l^i being unit vectors, mutually orthogonal relative to Finsler metric tensor, $g_{ij}(x, y)$. Such unit vector fields always exist in Finsler geometries of dimensions two (provided, $C \neq 0$).

Corollary 3. *If Q is constant, then, Q_i, Q_{ij} and R , all vanish so that*

$$D^* \rho = D\rho - 2y^h \delta_h \rho - 2C^v \dot{\partial}_v \rho - \frac{I^2}{2F^2} \rho. \quad (24)$$

Furthermore, a Berwald geometry with $R = 0$ can be transformed via a non-singular coordinate change, $x \rightarrow \tilde{x}$, to another so F becomes independent

of $\tilde{x}$, that is, $F(x, y) = F(\tilde{y})$. It follows for the undeformed (i.e., normal) model case that $Q(\tilde{x}, \tilde{y}) = 0$ in (8), so that (24) holds. Similar statements hold for the deformed case except the Finsler function $F(\tilde{y})$ is a different one than the undeformed case, [2].

Using the standard technique called the Cameron-Martin- Girsanov drift transformation, we construct an auxiliary Markov diffusion process $\{\xi(S), \eta(S)\}$, with which we can explicitly compute the probability density, $\rho = \rho(S, x, y)$, by the Feynman-Kac method. It is given the expectation

$$\rho = \mathbb{E} \left\{ \chi_{\{\tau > S\}} \rho_0(\xi(S), \eta(S)) \exp \left[\int_0^S V(\xi(u), \eta(u)) du \right] \right\}, \quad (25)$$

where $\xi(0) = x, \eta(0) = y, z(0) = z$, χ is the indicator function, [so has value 1 on the indicated set: $\{\text{times before first hitting to the surface, } y^1 y^2 = 0\}$, denoted τ and value zero for times after, $\tau = \tau_{x,y}$, for the process $\eta(S)$]. Note that $\tau = \tau_{x,y}$ depends on the path $(x(S), y(S))$ of the auxiliary Markov process which has the description

$$\begin{cases} d\xi^i = z_j^i * dw^j + e^i(\xi, \eta) dS, \\ d\eta^i = z_j^i * dv^j + f^i(\xi, \eta) dS, \\ dz_j^i = -G_{kl}^i(\xi, \eta) z_j^l * d\xi^k - C_{kl}^i z_j^l * d\eta^k, \end{cases} \quad (26)$$

$$e^i = -2y^i - 4g^{ij}Q_j \text{ and } f^i = -2C^i. \quad (27)$$

There is a substantial amount of information in the Feynman-Kac potential. For one thing, the important role of the Berwald-Gauss curvature R with its sign, is obvious from (24). Recall that, R , is a scalar function, so maps points in x -space to real numbers and its value is independent of coordinate choices as it is an invariant of the surface geometry of production space.

Generally, fixing all parameters except, R , the positivity of R , will increase $\rho(S, x, y)$, while a negative, R , decreases it. Such behaviour is consistent with the well-known results on Riemannian exit times: negative Riemannian curvature results in shorter average durations before first exit out of standard unit diameter disks, starting from their centers, while the reverse is true for positive Riemannian curvature. These results and others can be applied to the Sasaki-lift embedding of our Finslerian diffusion.

Remark 4. For an arbitrary Finsler geometry of 2 dimensions $n = 2$ the coefficients G_{jk}^i are functions of the F/L -ratio, i.e., y^2/y^1 . We will consider

this case in a future paper. For Berwald geometries, which is what we are considering here, the G coefficients do not depend on y , only on x . For the Berwald diffusions generated by, D or D_0 , the dependence on F/L is in the metric tensor g^{ij} which is homogeneous of 0-degree in y , so is a smooth function of x and of, $z = y^2/y^1$, the F/L -ratio, itself.

Finally, we show the direct effect that the F/L -ratio has on J -stability, i.e., $R > 0$. It is well-known that R is 0-degree in y , therefore, it is a function of x and of the F/L -ratio, z , and from the general theory, the Finsler-Bianchi identity for Berwald metrics holds true:

$$\partial_z R = -2R,$$

which shows that as the F/L -ratio, z , increases, J -stability, R , decreases. Furthermore, solving (18) yields, the positive expression

$$R = h(x) \exp\{-2z\},$$

where $h(x)$ is positive, but must be determined from the particular case. The question of what the function, $h(x)$, actually is does not matter here. We conclude generally that for positive, R , J -stability decreases with increasing F/L -ratio. This property holds for all time.

3. Stochastic Canalization and Sojourn Time

Noisy perturbations of the deterministic equations, which assume, $R > 0$, result in slowing down the motion along random trajectories, relative to white noise perturbations. It may be surprising that the condition, $R > 0$, decreases the probability that the random path stays close to its associated smooth trajectory. This can be viewed as a relaxation of canalization.

An Aside 5. To help understanding this, imagine a bee flying randomly around a flower bed in a fixed interval of time, $[0, T]$. It will be twisting and turning, stopping at a flower momentarily, only to start its random motion afresh in the next instant. That bee is in no hurry to rush off in any particular direction, so its foraging can be modelled as Brownian motion, but one that is a slower version than when there are no flowers present. Positive curvature encodes this slowdown. We can say canalization is not enforced.

On the other hand, R negative, results in a relative speed-up of random trajectories, and may be surprising, as it causes increase in the likelihood that a random path will stay close, in the time interval, $[0, T]$, to its deterministic counterpart, a geodesic, [20]. This is enforced canalization.

An Aside 6. Try to imagine our bee making a “bee line” for some intruder to its hive. Its trajectory will be fast and a bit erratic, but it will be close to a straight line.

Negative, R , tends to increase speed along the random path and simultaneously keeps it closer to the given smooth trajectory than white noise would do, even though the smooth trajectory itself tends to diverge from its smooth neighbors because, $R \leq 0$. Finally, it is known that a random path of a Riemannian Brownian motion on a closed 2-dimensional manifold with negative curvature, R , bounded below, will converge on a unique geodesic. Of course, in the present case the simplest example is 4-dimensional.

However, properties involving R are not the whole story on stochastic canalization. There are the drift terms in (21). For example, the divergence of the Cartan torsion, $\text{Div}(C)$, enters the sojourn probability formula and even if, $R = 0$, as above, the scalar, $\text{Div}(C)$, will provide stochastic canalization provided it is negative-valued. If it is positive-valued, the random path will wander away from its associated geodesic in the interval, $[0, T]$, sooner, rather than later.

We are nearly ready to give the sojourn formula, but first let us introduce the concept of vigour, ν , defined as

$$2\nu = \frac{1}{6}R + \text{Div}(C). \quad (28)$$

One sees that vigour is positive, if and only if, the sum of R and $\text{Div}(C)$ is negative and it may be positive in one open region and negative in another. It is possible, in principle, that one or the other of R and $\text{Div}(C)$ is positive while their sum is still negative in an open region. There is still another factor which enters into the determination of the sojourn probability.

It is the energy, ε , along, a (geodesic) solution, $\gamma \in TM$, solving (10). It is given by the positive quantity

$$g_{ij}(x, y) \left[\left(\frac{dy^i}{dS} \right)_{\gamma} - C^i \right] \left[\left(\frac{dy^j}{dS} \right)_{\gamma} - C^j \right] = 2\varepsilon. \quad (29)$$

For a diffusing path, X_t , starting at $\gamma(0) = x$, the Sojourn Probability, P_h , to stay in a tube of small radius $h \searrow 0$ around geodesic solution of (10), $\gamma(S)$, up to time T is

$$P_h \{ \text{dist}_G(X_t, \gamma_t) < h \} = a \exp\{-bT\} \exp \left\{ - \int_0^T (\varepsilon + \nu) \, dt \right\}. \quad (30)$$

The positive constants a and b are from the eigen-structure of the 4-dimension Euclidean Laplacian, a basic object of reference, but we will not need to know their exact values, [20]. Now let us compute ν for the normal and deformed models. We know that $R = 0$ so we need only compute $\text{Div}(C)$. This is given, using the Berwald basis of, (19), (20), (21) to be

$$\text{Div}(B) = \frac{1}{g} \delta_i(g \, y^i) + \frac{1}{g} \dot{\partial}_i(g \, C^i), \quad (31)$$

where $\sqrt{G} = g$, and we use the existence of a coordinate system for which F depends only on y^i , guaranteed by, $R = 0$, and these coordinates exist for both the normal and deformed dynamics. This means $\delta_i = \partial_i$ and consequently the first term in (31) vanishes. We now split the remainder of the proof into sections, one for Normal and one for Deformed.

Case 7 (Normal). In this case,

$$\det(g_{ij}) = \exp(4y^2/y^1). \quad (32)$$

We use the orthonormal frame $\{l^i, m^i\}$ for the normal case,

$$F(y) = y^1 \exp\{2y^2/y^1\}$$

and recall

$$\begin{cases} C^i = -\frac{1}{2}(I/F) \, m^i, \\ m^1 = -l_2/\sqrt{\det(g_{ij})}, \\ m^2 = l_1/\sqrt{\det(g_{ij})}, \, l_i = \dot{\partial}_i \, F. \end{cases} \quad (33)$$

The principal scalar, $I = 2$, for the case at hand (having chosen the positive orientation). Furthermore, we compute

$$m^1 = -\exp\{-y^2/y^1\} \quad \text{and} \quad m^2 = (1 - y^2/y^1) \exp\{-y^2/y^1\}, \quad (34)$$

and finally, after taking partial derivatives, obtain

$$\text{Div}(C) = -\frac{2}{(y^1)^2} \exp(-2y^2/y^1). \quad (35)$$

Case 8 (Deformed). What is different here is $F(y)$ and $\det(g_{ij})$. The formulas in (33) are general and we now adapt them to the case at hand. As before, the first term in (31) vanishes. So

$$F(y) = y^2 \left(\frac{y^2}{y^1} \right)^{1/\lambda}, \quad \det(g_{ij}) = \left[\frac{(\lambda+1)}{\lambda^2} \right] \left(\frac{y^2}{y^1} \right)^{2+4/\lambda}. \quad (36)$$

We compute

$$\begin{cases} m^1 &= -\sqrt{\lambda+1} \left(\frac{y^1}{y^2} \right)^{1+1/\lambda} \\ m^2 &= -\frac{1}{\sqrt{\lambda+1}} \left(\frac{y^1}{y^2} \right)^{1/\lambda} \end{cases}. \quad (37)$$

And finally, after taking partial derivatives,

$$\text{Div}(C) = -\left(1 + \frac{2}{\lambda}\right) \left(\frac{1}{\lambda}\right) \left(\frac{\lambda+2}{\lambda+1}\right) \left(\frac{1}{y^2}\right)^2 \left(\frac{y^1}{y^2}\right)^{2/\lambda}. \quad (38)$$

Since, $\nu = \frac{1}{2}\text{Div}(C)$, we have proved stochastic canalization.

Remark 9. For the deformed system with large initial growth rate, λ , for the cell populations, canalization strength is diminished and is inversely proportional to that rate, λ , and inversely proportional to the square of the adipose biomass, $(y^2)^2$, provided the F/L ratio is constant. Both diminish the strength.

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