

Fractal Structure and Storage Dynamics of Glycogen

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Abstract: Fractals are complex structure which can be characterized in a compact form using least amount of information. The fact that nature has applied very simple rules to provide optimal space filling structures and dynamical efficiency is already known to researchers. Glycogen storage is such an example of dynamical efficiency and self-similar structure. This paper provide a model for the storage dynamics of glycogen, suggesting that the fractal structures leads to phase constancy in the growth dynamics.

Keywords: glycogen, fractals, systems biology, self-organized critically

1. INTRODUCTION

Nature has found many ways to make the living beings the best examples of optimization. This means that nature offers simple but effective procedures to produce structures by means of most economic way. One of such procedures is that of branching a structure by means of simple mathematical rules, often called fractal dimensions (Mandelbrot, 1983). As such, there are many systems already known to be fractals and recognized as posing specific properties. Some of these structures are: the capillary system (Elzbieta et al., 2005), the respiratory system (Muntean et al., 2009; Ionescu et al., 2009b), the leaves (Ionescu and Tenreiro Machado, in print), etc. It can also be observed that corals (i.e. brain corals) and cells have much in common, they are both fractals (Ainsworth, 2009). The reason waving together these examples is that a huge amount of contact surface can be generated in a compact volume.

Glycogen is one of the most important fuel supplier in living organisms (Melendez et al., 1999), in the form of stored glucose. It is a highly branched structure, playing a metabolic role (?). Its function is to provide a large amount of glucose in a very short time. Such demands are necessary when quick movements are required, e.g. during exercise. After ingestion of a meal containing carbohydrates, conversion of glucose into glycogen in muscle, fat and liver is a key event in the maintenance of glucose homeostasis. Conversely, in the fed-to-fasted transition, glycogen storage represents a major source of energy and serves to protect against hypoglycemia. Liver glycogen storage is reduced jointly with an increase in hepatic glucose production in all forms of human diabetes studied hitherto (Newgard et al., 2000). Muscle glycogen deposition is also impaired in type 2 diabetes (Nikoulina et al., 2000). These metabolic perturbations clearly contribute to the development of hyperglycemia and may be a site of therapeutic intervention. Hence, it is important to provide compact models for glycogen which capture its metabolic dynamics.

The concept of fractional order – or non-integer order – systems refers to those dynamical systems whose model parameters contain arbitrary order derivatives and/or integrals. The fractional order derivatives and integrals are tools of the Fractional Calculus theory (Podlubny, 1999). The dynamical systems whose model can be approximated in a natural way using fractional order terms, exhibit specific features:

- viscoelasticity;
- diffusion;
- fractal structure.

The fractal structure of the glycogen has been proven in terms of its intrinsic properties (Melendez et al., 1999). This paper attempts to bring further the concept of fractal structure in the glycogen structure in terms of its growth dynamics, i.e. molecular volume. Since the glycogen synthesis is an active process, glycogen metabolism plays an important role. This paper will present a linear simplistic model able to capture its intrinsic self-similar structure (fractal) and shows that the features of the glycogen molecule lead to the appearance of a constant-phase dynamics.

The paper is organized as follows: the role of glycogen is discussed in the next section, along with the static and dynamic models for its growth and metabolism respectively. Results are presented in section 3, along with short discussion. The main outcome of this investigation is summarized in a conclusion section.

2. ROLE AND MODELS OF THE GLYCOGEN MOLECULE

2.1 Volume of Glycogen Molecule

The role of glycogen is to provide a high amount of energy (glucose) whenever needed in short time intervals. The glycogen molecule can be described using complex chemical reactions triggered by various chemical stimuli. The liver will break-down glucose in blood and host changes

in the concentration of different metabolites and intermediates in the blood and tissue compartments. The convection and transport of glycogen between the blood and tissue compartments requires a hybrid system, containing both continuous states as well as discrete states (on-off switches). The model may also contain a delay, introduced by the time required for neuronal stimulation onset whenever synthesis/degradation of glycogen is employed (Clouties et al., 2009).

Glycogen synthesis and degradation are tightly regulated by hormones and metabolic signals, primarily via modulation of glycogen synthase and glycogen phosphorylase enzymatic activities (Newgard et al., 2000; Damiani, 2005; Ball et al., 1996).

The mathematical model describing the volume of glycogen (V_S) is given by (Melendez et al., 1999):

$$V_S = \frac{4}{3}\pi \cdot t^3 \cdot (0.12g_c + 0.35)^3 \quad (1)$$

with t the number of tiers (max. 12) and g_c the chain length (=13). The branching degree as discussed in (Melendez et al., 1999) has been assumed here to be equal to 2 (dichotomous structure). Figure 1 depicts schematically the structure of the glycogen molecule, similarly to a Koch tree representation (Melendez et al., 1999).

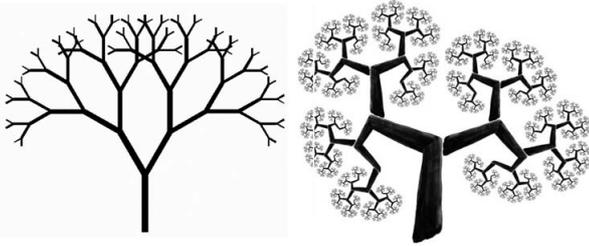


Fig. 1. Schematic representation of the Koch tree.

In this manner, the glycogen can store the maximum amount of glucose in the most possible dense molecule. It is such that this growth is regulated by the neural activity in the brain, as a background process (?). It has been shown that most of the biological processes and structures in the living organisms pose two important features: self-organized criticality, fractal structure. The one feature is related to the other; i.e. the property of continuously adapting and changing one's dynamics requires fractal structure to some degree. The glycogen poses one property: fractal structure. The purpose is to show that it enables the second, more important, property: self-organized criticality. This implies that according to the needs of the organism, the storage dynamics change to meet the demands.

2.2 Underlying Principles of Fractional Calculus

The fractional calculus is a generalization of integration and derivation to non-integer (fractional) order operators. At first, we generalize the differential and integral operators into one fundamental operator D_t^n (n the order of the operation) which is known as *fractional calculus*.

Several definitions of this operator have been proposed (see, e.g. (Podlubny, 1999)). All of them generalize the standard differential-integral operator in two main groups:

- they become the standard differential-integral operator of any order when n is an integer;
- the Laplace transform of the operator D_t^n is s^n (provided zero initial conditions), and hence the frequency characteristic of this operator is $(j\omega)^n$.

A fundamental D_t^n operator, a generalization of integral and differential operators (*differintegration* operator), is introduced as follows:

$$D_t^n = \left\{ \begin{array}{ll} \frac{d^n}{dt^n}, & n > 0 \\ 1, & n = 0 \\ \int_0^t (d\tau)^{-n}, & n < 0 \end{array} \right\} \quad (2)$$

where n is the fractional order and $d\tau$ is a derivative function. Since the entire thesis will focus on the frequency-domain approach for fractional order derivatives and integrals, we shall not introduce the complex mathematics for time domain analysis. The Laplace transform for integral and derivative order n are, respectively:

$$L\{D_t^{-n}f(t)\} = s^{-n}F(s) \quad (3)$$

$$L\{D_t^n f(t)\} = s^n F(s) \quad (4)$$

where $F(s) = L\{f(t)\}$ and s is the Laplace complex variable. The Fourier transform can be obtained by replacing s by $j\omega$ in the Laplace transform and the equivalent frequency-domain expressions are:

$$\frac{1}{(j\omega)^n} = \frac{1}{\omega^n} \left(\cos \frac{\pi}{2} + j \sin \frac{\pi}{2} \right)^{-n} = \frac{1}{\omega^n} \left(\cos \frac{n\pi}{2} - j \sin \frac{n\pi}{2} \right) \quad (5)$$

$$(j\omega)^n = \omega^n \left(\cos \frac{\pi}{2} + j \sin \frac{\pi}{2} \right)^n = \omega^n \left(\cos \frac{n\pi}{2} + j \sin \frac{n\pi}{2} \right) \quad (6)$$

Thus, the modulus and the argument of the FO terms are given by:

$$Modulus(dB) = 20 \log |(j\omega)^{\mp n}| = \mp 20n \log |\omega| \quad (7)$$

$$Phase(rad) = arg((j\omega)^{\mp n}) = \mp n \frac{\pi}{2} \quad (8)$$

resulting in:

- Magnitude (dB vs log-frequency): straight line with a slope of $\mp 20 \cdot n$ passing through 0dB for $\omega = 1$;
- Phase (rad vs log-frequency): horizontal line, thus independent with frequency, with value $\mp n \cdot \frac{\pi}{2}$.

2.3 A Proposed Model for the Storage Dynamics of Glycogen

There are models existing in the literature for glycogen storage, including the dynamics, regulatory response of the glycogen pool and its integration in the energy metabolism in brain (Clouties et al., 2009), in muscles (Greenberg et al., 2006), etc. Models include switches to account for changes in biological behaviour, i.e. metabolic regulation. In fact, theory presents the glycogen pool as a dynamic energy reserve. Energetic potential travels through the players of such a glycogen storage system; a schematic example of glycolysis is given in figure 2.

By means of electrical analogy, simplified models could be derived and used in simulations. Glycogen is not considered to be an infinite substrate pool, but rather a dynamic

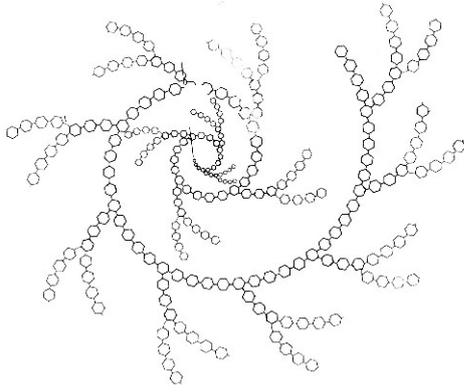


Fig. 2. Schematic representation of the glycogen molecules.

energy reserve which the tissue can use to buffer its energy budget between low/high demand periods.

The growth/storage of glycogen can be used with compact functions, such as fractional order models. Take for instance, the model of a molecule of glycogen as being represent by a series electrical resistance R_e with an electrical capacitor C_e . This representation of a glycogen molecule level is based on the metabolic dynamics: storage (capacitor) and dissipation (resistance).

In fractal geometry, the fractal dimension, D_f , is a statistical quantity that gives an indication of how completely a fractal appears to fill space, as one zooms down to finer and finer scales. The fractal dimension for such a structure is $D_f = 2$ (Melendez et al., 1999). This implies that although the number of glucosidic chains ends (points of phosphorylase attack for glycolysis) is a dimension zero object, in the limit of infinite iterations, the structure increases until it covers the entire surface of a spherical molecule. On the surface provided by the terminal ends, the enzymes can set to work. This result shows that glycogen synthesis is a mechanism which ensures generation of a structure with the maximum possible compacticity. This then represents the very core of optimization. However, in practice, the number of iterations in glycogenesis is not infinite.

The equivalent structure of the glycogen molecules from figure 2 can be depicted as in figure 3. Only the first 4 tiers of the total 12 are here represented.

From symmetry, we have that the same amount of glycogen chains are on each side of the structure; hence, the network from figure 3 can be compacted into one ladder network with cells corresponding to each level (denoted by the tiers) in the original representation. In this manner, although each element will be the same, a ratio from one level to another will be introduced in the ladder, i.e. dependent on the number of branches.

We shall consider that this generic ratio is greater than 1 (for growth) and depends on the ratios between consecutive branches of glycogen molecules. Suppose the ratio of R_e from one molecule to the next molecule is λ and the ratio for C_e is χ .

The general recurrence form of such a compacted ladder network in terms of its the total admittance $F(s)$ with

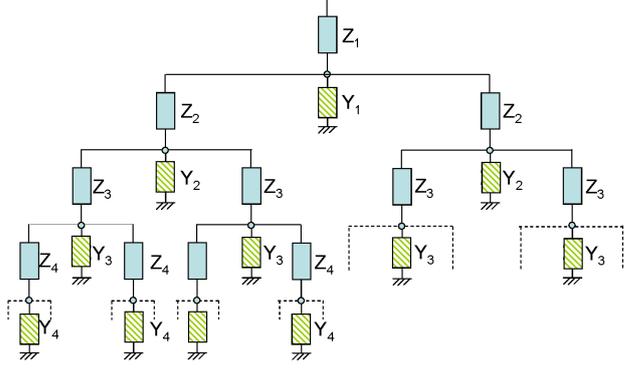


Fig. 3. Schematic representation of the glycogen molecules in an equivalent tree. Z represents the impedance of the longitudinal branch and Y represents the impedance of the transversal branch.

$m = N$ tiers, for $N \rightarrow \infty$ (Ionescu et al., in print):

$$F(s) = \frac{1/(R_{e1})}{1 + \frac{1/[C_{e1}sR_{e1}]}{1 + \frac{1/[C_{e2}sR_{e2}]}{1 + \frac{1/[C_{e2}sR_{e3}]}{1 + \dots \frac{1/[C_{e(N-1)}sR_{eN}]}{1 + 1/[C_{eN}sR_{eN}]}}}} \quad (9)$$

which, in terms of the recursive ratios, can be re-written as:

$$F(s) \cong \frac{1/R_{e1}}{1 + \frac{1/R_{e1}C_{e1}s}{1 + \frac{1/\lambda R_{e1}C_{e1}s}{1 + \frac{1/\chi \lambda R_{e1}C_{e1}s}{1 + \frac{1/\chi \lambda^2 R_{e1}C_{e1}s}{\dots \frac{1/\chi^{N-2} \lambda^{N-1} R_{e1}C_{e1}s}{1 + 1/\chi^{N-1} \lambda^{N-1} R_{e1}C_{e1}s}}}}}} \quad (10)$$

If we introduce the notations:

$$W_d(s) = \frac{1}{R_{e1}C_{e1}s}, \quad W_n(s) = \frac{1}{R_{e1}}, \quad (11)$$

then (10) can be reduced to an analogue representation:

$$F(s) \approx \frac{W_n(s)}{1 + g(W_d(s), \lambda, \chi)} \quad (12)$$

in which $g(W_d(s), \lambda, \chi)$ denotes:

$$g(W_d(s), \lambda, \chi) = \frac{W_d(s)}{1 + \frac{W_d(s)/\lambda}{1 + \frac{W_d(s)/\lambda\chi}{1 + \frac{W_d(s)/\lambda^2\chi}{\dots}}}} \quad (13)$$

Since $W_d(s)$ can be taken in front of the expansion and both λ and χ are constants, we can write that:

$$F(s) \approx \frac{W_n}{K(\lambda, \chi)(W_d(s))^n} \quad (14)$$

with the fractional order n given by

$$n = \frac{\log(\lambda)}{\log(\lambda) + \log(\chi)} \quad (15)$$

or that, in our specific case:

$$F(s) \cong \frac{1/R_{e1}}{K(\lambda, \chi) \cdot (1/R_{e1} C_{e1} s)^n} \quad (16)$$

The values for $K(\lambda, \chi)$ can be determined as described in (Oustaloup, 1995); since we do not make use of it explicitly, its derivation will not be discussed here. Moreover, our sole purpose was to show that the continuous fraction expansion from (9) will lead to a compact form which contains a term in the fractional-order n . Hence, relation (16) shows the link between the ladder network from figure 3 and the appearance of a fractional order term in the form of total admittance. In the frequency domain (i.e. frequency has the meaning of storage rate), the fractional order will lead to a constant-phase behaviour, i.e. a phase-locking in the frequency range given by the convergence conditions (Oustaloup, 1995). Depending on the number of tiers in the molecule (N) and their ratios, the constant-phase behavior will emerge over a specific range of frequencies.

3. RESULTS AND DISCUSSION

The volume of a molecule of controlled structure of glycogen synthesis from (??) is given in figure 4. The controlled rate of branching degree ($r=2$) results in a linear log-log growth, which is a hallmark of fractal structures. The amount of 10^5 volume (in nm^3) results from optimizing the parameters of the glycogen molecule to the actual cellular glycogen values (Melendez et al., 1993). In such a structure, there will be about 55000 glucose residues in the 13th tier. The fact that the surface of the glucose residues grows exponentially of power 2, becoming more and more crowded on the molecule surface, suggests a self-limitation property of such a structure.

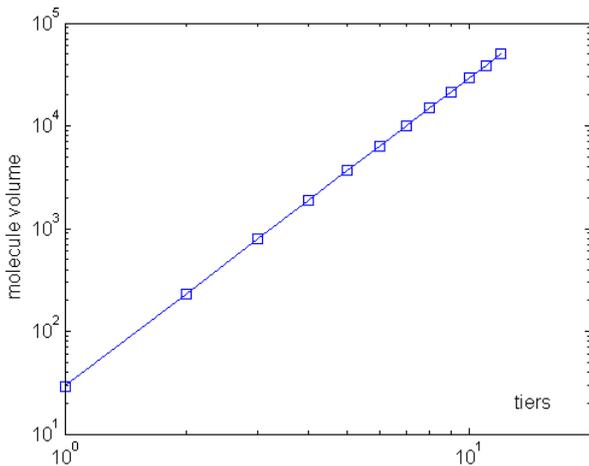


Fig. 4. Volume of a branching rate $r = 2$ glycogen molecule; arbitrary units.

In disease, this rate becomes uncontrolled and the volume of glycogen synthesis grows exponentially, leading to aberrant hepatic glucose output and to hyperglycemia in diabetes. The results obtained in figure 5 for increasing branching degrees, suggests that although the glucogen storage increases, there is a threshold upon which this volume will become independent on the branching rate

r . That is, no matter how much r will increase, the change in the volume becomes insignificant.

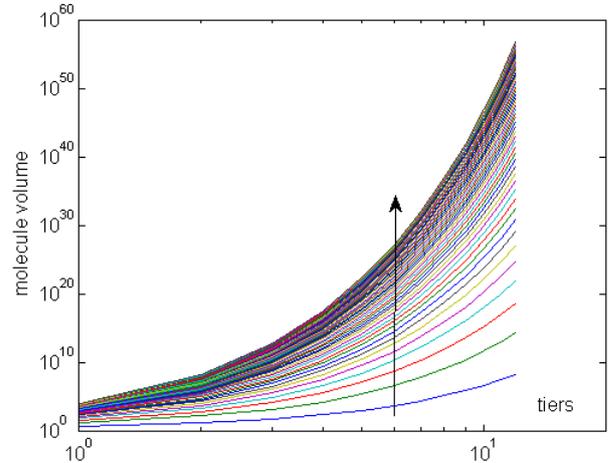


Fig. 5. Volume of increasing branching rates $r = 2 - 50$ for glycogen molecules. Arrow indicates the evolution with increasing values of r ; arbitrary units.

The result from (16) implies a sort of conservation of dynamics independent on the frequency of the stimulus (for storage or breakdown). For equal rates of $\lambda = \chi$, the fractional order of the Laplace operator from (15) becomes equal to 0.5. This means that independent on the number of tiers and on the values for R and C , the phase will be constant at $0.5 \cdot 90^\circ = 45^\circ$. Similarly, the value for the magnitude will decrease with a value of $0.5 \cdot 20dB/dec = 10dB/dec$. This is then equivalent to the illustrative example from figure 6.

The presence of the constant-phase suggests that the glycogen growth dynamics (in terms of stimulus, which in turn can be related to a frequency) are controlled by a stable neural dynamics. This ensures that at any time, the process of glycogen storage can take place, un-affected by external stimuli, unless a certain threshold of information has been reached (?).

Such constant phase dynamics are a hallmark of fractal dynamical systems. In practice, it means that nature has provided a high robustness against various stimuli within the hormonal regulation of such a chemical chain of interactions. It is therefore an equilibrium providing a high efficiency and low sensitivity to disturbances. Nevertheless, this equilibrium can be lost; the major cause is then a DNA mutation which accounts for major changes in the original structure (Wang et al., 2007). In this case, another hallmark of fractals is their capability to self-organize. That is, whenever necessary, the original structure can change its local functionality to maintain the overall function unperturbed (Ainsworth, 2009). Hence the nucleus of the molecule plays an important role, by altering the fractal structure and adapting its dynamics to the functional requirements.

The self-organized criticality recognized in the neuroscience shows that metabolic processes such as the one of glycogen storage, are in fact background phenomena in the cortical activity and are continuously adapting as a

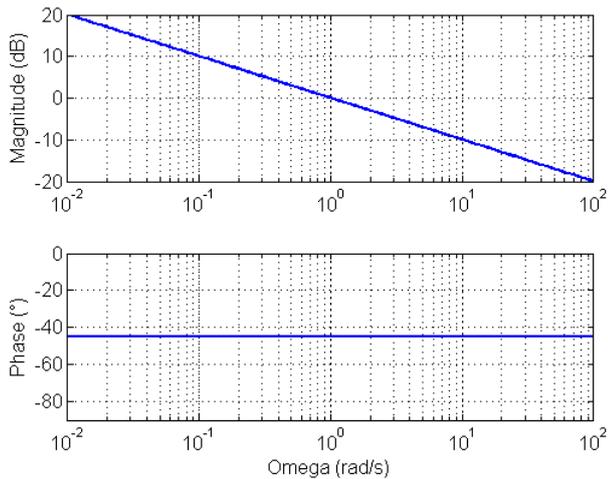


Fig. 6. The impedance (inverse of admittance) of the glycogen dynamics; the input is a stimulus with a given frequency, the output is the energy metabolism by means of gain and phase.

function of ambient information. For instance, if a person with a certain lifestyle requires more energy supply (e.g. athletics) then the growth rate, hence constant-phase behavior will be changed to another value. At the moment that a maximum volume is reached with respect to the number of branching rates, then the structure may break and re-arrange itself in a different branching geometry, leading to different dynamics (i.e. different values for the constant-phase).

4. CONCLUSION

In this paper, the fractal structure of the glycogen molecule has been discussed with respect to its storage dynamics. A compact model based on its intrinsic properties: self-similarity, recurrence and self-organization has been presented. The consequence of such a dynamical system is the constant-phase behavior, a hallmark for fractal dynamical structures. This implies a preservation of energy efficiency which is frequency-independent with hormonal stimulus. Without claiming the direct use of the proposed model in biology, its structure and its result may suggest a possible mechanism for the storage dynamics.

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