# Effect of Vitamin D on Bone Formation and Resorption: Mathematical Modeling Approach

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***Abstract*—**We study the effect of Vitamin D on bone formation and resorption processes by developing a system of nonlinear differential equations. The model accounts for the serum level of vitamin D, the number of active osteoclastic cells and the number of active osteoblastic cells. It is then investigated both theoretically and numerically. The numerical result shows that the model can exhibit a periodic behavior for the parameters chosen to satisfy the conditions that we derived theoretically in conforming to the pulsatile serum level of vitamin D which has been observed clinically.

***Keywords*—**bone formation, bone resorption, limit cycle, mathematical model, vitamin D.

## I. Introduction

VITAMIN D plays an important role in the regulation of mineral homeostasis and the bone formation and resorption processes [1]. The biological active form of vitamin D is calcitriol. Calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR), which is principally located in the nuclei of target cells [2]. In bone formation and resorption process, calcitriol interacts with its VDR in osteoblast (bone forming cell) resulting in the expression of RANKL which recognized by its corresponding receptor RANK on the preosteoclast. The interaction of RANKL and RANK results in signal transduction inducing the preosteoclast to be come a mature osteoclast (bone resorbing cell) [3]-[5].

The aims of bone formation and resorption processes are to regulate calcium homeostasis, to repair micro-damaged bones (from everyday stress) and also to shape and sculpture the skeleton during growth [6]-[8]. In this paper, we will propose a mathematical model to describe bone formation and resorption processes based on the effect of vitamin D.

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## II. A Mathematical Model

We now proceed to propose a nonlinear mathematical model to describe bone formation and resorption processes based on the effect of vitamin D as follows. Let us denote the serum level of vitamin D at time $t$ by $X(t)$, the number of active osteoclasts at time $t$ by $Y(t)$, and the number of active osteoblasts at time $t$ by $Z(t)$. At first, we assume that the high levels of osteoclast and osteoblast precursors lead to the high levels of active osteoclastic and osteoblastic cells, respectively, which result from the differentiation, and activation of their precursors.

The major biological function of vitamin D is to maintain the serum calcium in the normal physiological range to preserve neuromuscular and cellular functions [9]. Vitamin D maintains the blood calcium in the normal range by enhancing the efficiency of intestinal calcium absorption and by increasing the mobilization of stem cells to become osteoclasts that, in turn, mobilize calcium stores from bone [9]-[12]. Therefore, the equation for the rate of change in serum level of vitamin D is then assumed to have the form

$$\frac{dX}{dt} = \frac{a_1}{k_1 + Y} - b_1 X \tag{1}$$

where the first term on the right-hand side of (1) represents the rate of change in serum level of vitamin D which decreases with the increase in the number of active osteoclastic cells in order to counter balance the high level of calcium in blood resulted from the large number of active osteoclastic cells. The last term is the removal rate constant $b_1$. $a_1$ and $k_1$ are positive constants.

Osteoclasts are bone resorbing cells originated from hemopoietic stem cells of the monocyte/macrophage lineage [13]. The differentiation and activation of osteoclasts are regulated by osteoblasts [14], [15] requiring several factors such as osteoclast differentiation factor (ODF) which was found to be identical to receptor activator NF-kB ligand (RANKL) [14], [16], [17]. Therefore, the dynamics of the active osteoclastic population can be described by the following equation

$$\frac{dY}{dt} = \left( \frac{a_2 + a_3 X}{k_2 + X^2} \right) YZ - b_2 Y \tag{2}$$

where the first term on the right-hand side of (2) represents the stimulating effect of vitamin D on the reproduction of active osteoclasts. Vitamin D interacts with its VDR in osteoblast resulting in the expression of RANKL which recognized by its corresponding receptor RANK on the preosteoclast. The interaction of RANKL and RANK results in signal transduction inducing the preosteoclast to be come a mature osteoclast [3]-[5]. The last term is the removal rate constant $b_2$. $a_2, a_3$ and $k_2$ are positive constants.

Osteoblasts are bone forming cells derived from the mesenchymal stem cells. The proliferation and differentiation of osteoblasts involve many factors such as FGF, IGF-I, TGF-beta [18]. On the other hand, vitamin D has been found to stimulate the reproduction of active osteoblastic cells [19]. The dynamics of the osteoblastic population can be described by the following equation

$$\frac{dZ}{dt} = a_4 + \frac{a_5 XZ}{k_3 + X} - b_3 Z \tag{3}$$

The first term on the right-hand side of (3) represents the reproduction of active osteoblasts by many factors such as FGF, IGF-I, TGF-beta. The second term represents the stimulating effect of vitamin D on the reproduction of active osteoblastic cells. The last term is the removal rate constant $b_3$. $a_4, a_5$ and $k_3$ are positive constants.

## III. SINGULAR PERTURBATION ANALYSIS

We assume that Vitamin D has the fast dynamics. The osteoclastic population possesses the intermediate dynamics and the osteoblastic population has the slow dynamics. Consequently, we scale the dynamics of the three components and parameters of the system in term of small positive parameters $0 < \varepsilon << 1$ and $0 < \delta << 1$ as follows.

Letting $x = X$, $y = Y$, $z = Z$, $c_1 = a_1$, $c_2 = \frac{a_2}{\varepsilon}$, $c_3 = \frac{a_3}{\varepsilon}$, $c_4 = \frac{a_4}{\varepsilon\delta}, c_5 = \frac{a_5}{\varepsilon\delta}, d_1 = b_1, d_2 = \frac{b_2}{\varepsilon}, d_3 = \frac{b_3}{\varepsilon\delta}$, we are led to the following model equations:

$$\frac{dx}{dt} = \frac{c_1}{k_1 + y} - d_1 x \equiv f(x, y, z) \tag{4}$$

$$\frac{dy}{dt} = \varepsilon\left(\left(\frac{c_2 + c_3 x}{k_2 + x^2}\right) yz - d_2 y\right) \equiv \varepsilon g(x, y, z) \tag{5}$$

$$\frac{dz}{dt} = \varepsilon\delta\left(c_4 + \frac{c_5 xz}{k_3 + x} - d_3 z\right) = \varepsilon\delta h(x, y, z) \tag{6}$$

The shapes and relative positions of the manifolds $\{f = 0\}, \{g = 0\}$ and $\{h = 0\}$ determine the shapes, directions and speeds of the solution trajectories. We now analyze each of the equilibrium manifolds in detail.

***The manifold*** $\{f = 0\}$

This manifold is given by the equation

$$x = \frac{1}{d_1}\left(\frac{c_1}{k_1 + y}\right) \equiv A(y) \tag{7}$$

which is independent of the variable *z* and thus parallels to the z-axis. It intersects the $(x,z)$ – plane along the line

$$x = \frac{c_1}{d_1 k_1} \equiv x_1 \tag{8}$$

Moreover, $A(y)$ is a decreasing function of $y$ and $A(y) \to 0$ as $y \to \infty$.

***The manifold*** $\{g = 0\}$

This manifold consists of two submanifolds. One is the trivial manifold $y = 0$. The nontrivial one given by the equation

$$z = \frac{d_2\left(k_2 + x^2\right)}{c_2 + c_3 x} \equiv B(x) \tag{9}$$

this nontrivial manifold is independent of the variable y and thus this submanifold is parallel to the $y$-axis. It attains the relative minimum at the point where

$$x = \frac{-c_2 \pm \sqrt{c_2^2 + c_3^2 k_2}}{c_3} \equiv x_m \tag{10}$$

and

$$z = \frac{d_2\left(k_2 + x_m^2\right)}{c_2 + c_3 x_m} \equiv z_m \tag{11}$$

On the other hand, the nontrivial manifold intersects the (*y*,*z*)-plane along the line

$$z = \frac{d_2 k_2}{c_2} \equiv z_1 \tag{12}$$

Moreover, the manifold $\{f = 0\}$ intersects the trivial manifold $\{g = 0\}$ along the line $x = x_1$ on the (*x*,*z*)-plane and it intersects the nontrivial manifold $\{g = 0\}$ along the curve

$$z = \frac{d_2\left(k_2 + A(y)^2\right)}{c_2 + c_3 A(y)} \tag{13}$$

which has a relative minimum point $N(x_m, y_m, z_m)$ where

$$y_m = \frac{c_1}{d_1 x_m} - k_1 \tag{14}$$

Also, the curve $\{f = g = 0\}$ intersects the (*x*,*z*)-plane at the point *U* where $y = 0, x = x_1$ and

$$z = \frac{d_2\left(k_2 + x_1^2\right)}{c_2 + c_3 x_1} \equiv z_2 \tag{15}$$

***The manifold*** $\{h = 0\}$

This manifold is given by the equation

$$z = \frac{c_4 x + c_4 k_3}{(d_3 - c_5)x + d_3 k_3} \equiv C(x) \tag{16}$$

which is independent of the variable *y*, and thus parallels to the *y*-axis. It intersects the (*y*,*z*)-plane along the line

$$z = \frac{c_4}{d_3} \equiv z_3 \tag{17}$$

and intersects the (x,z)-plane along a curve which is asymptotic to the line

$$x = \frac{d_3 k_3}{c_5 - d_3} \equiv x_2 \tag{18}$$

We note that $x_2 > 0$ if and only if

$$d_3 < c_5 \tag{19}$$

We also observe that $C(x)$ is an increasing function of *x*.

Moreover, the trivial manifold $\{g = 0\}$ intersects the manifold $\{h = 0\}$ along the curve

$$z = \frac{d_2 (k_2 + x^2)}{c_2 + c_3 x}$$

on the (*x*,*y*)-plane and the nontrivial manifold $\{g = 0\}$ intersects the manifold $\{h = 0\}$ along the line

$$\left\{ x = x_3, z = \frac{c_4 x_3 + c_4 k_3}{(d_3 - c_5)x_3 + d_3 k_3} \equiv z_4 \right\}$$

which is parallel to the *y*-axis, $x_3$ being the real solution of

$$d_2 (d_3 - c_5)x^3 + (d_2 d_3 k_3 - c_3 c_4)x^2$$
$$+ (d_2 k_2 (d_3 - c_5) - c_2 c_4 - c_3 c_4 k_3)x + (d_2 d_3 k_2 k_3 - c_2 c_4 k_3) = 0$$

which exists in the positive octant and is unique provided that

$$\frac{c_2 c_4}{k_2} < d_2 d_3 < \frac{c_3 c_4}{k_3} \tag{20}$$

On the other hand, the manifold $\{h = 0\}$ intersects the (*x*,*z*)-plane along the curve $z = C(x)$ which intersects the line $x = x_1$ at the point $S_1(x_1, 0, z_5)$ where

$$z_5 = \frac{c_4 x_1 + c_3 k_3}{(d_3 - c_5)x_1 + d_3 k_3} \tag{21}$$

The curve $\{f = g = 0\}$ intersects the curve $\{g = h = 0\}$ at the point $S_2(x_3, y_1, z_5)$ where

$$y_1 = \frac{c_1}{d_1 x_3} - k_1 \tag{22}$$

**Theorem 1** Suppose inequalities (19) and (20) hold. If $\varepsilon$ and $\delta$ are sufficiently small and

$$x_m < x_3 < x_1 \tag{23}$$

and

$$z_3 < z_m < z_2 < z_5 < z_1 \tag{24}$$

where all the parametric values are given as above, then the system of (4)-(6) has a global attractor, in the positive octant of the phase space which is a limit cycle. The limit cycle can be constructed by concatenation of catastrophic various transitions occurring at three different speeds.

The proof of the theorem is based on geometric singular perturbation method [20], [21]. This method is a useful tool in the analysis of the different types of flows that clear separation in time scales: the fast flow, the intermediate flow, and the slow flow.

Under the conditions in Theorem 1, without loss of generality we start from point *I* and we assume that the position of *I* is as in Fig. 1 with $\{f \neq 0\}$. A fast transition will tend to point *J* on the manifold $\{f = 0\}$. Here, $\{g < 0\}$ and a transition at intermediate speed will be made in the direction of decreasing $y$ until point *K* on the curve $\{f = g = 0\}$ is reached. A slow transition then follows along this curve to some point *L* where the stability of submanifold will be lost. A jump to point *M* on the other stable part of $\{f = g = 0\}$ followed by a slow transition in the direction of decreasing z until the point *N* is reached since $\{h < 0\}$ here. Once the point *N* is reached the stability of submanifold will be lost. A jump to point *O* on the other stable part of $\{f = g = 0\}$ followed by a slow transition in the direction of increasing *z* since $\{h > 0\}$ here. Consequently, a slow transition will bring the system back to the point *L*, followed by flows along the same path repeatedly, resulting in the closed orbit *LMNOL*. Thus, limit cycle in the system for $\varepsilon$ and $\delta$ are sufficiently small exists.

## IV. NUMERICAL RESULT

A computer simulation of the system (4)-(6) with parametric values chosen to satisfy the condition in Theorem 1 is presented in Fig. 2. The solution trajectory, shown in Fig. 2a project onto the $(x, y)$-plane, tends to a limit cycle as theoretically predicted. The corresponding time courses of the level of serum vitamin D, the number of active osteoclasts and the number of active osteoblasts are as shown in Fig. 2b, 2c and 2d, respectively.

## V. CONCLUSION

In this paper we have studied the effect of vitamin D on bone formation and resorption processes by developing a system of nonlinear differential equations accounting for the level of vitamin D, the number of active osteoclasts, and the number of active osteoblasts as in (1)-(3). We then derived the conditions on the system parameters for which a limit cycle exists by applying the singular perturbation method. A computer simulation of the model is then carried out. The result shows that our model can deduce the nonlinear dynamic behavior which closely resembles to the serum level of vitamin D that has been observed clinically [22], [23], even though the model is kept relatively simple.

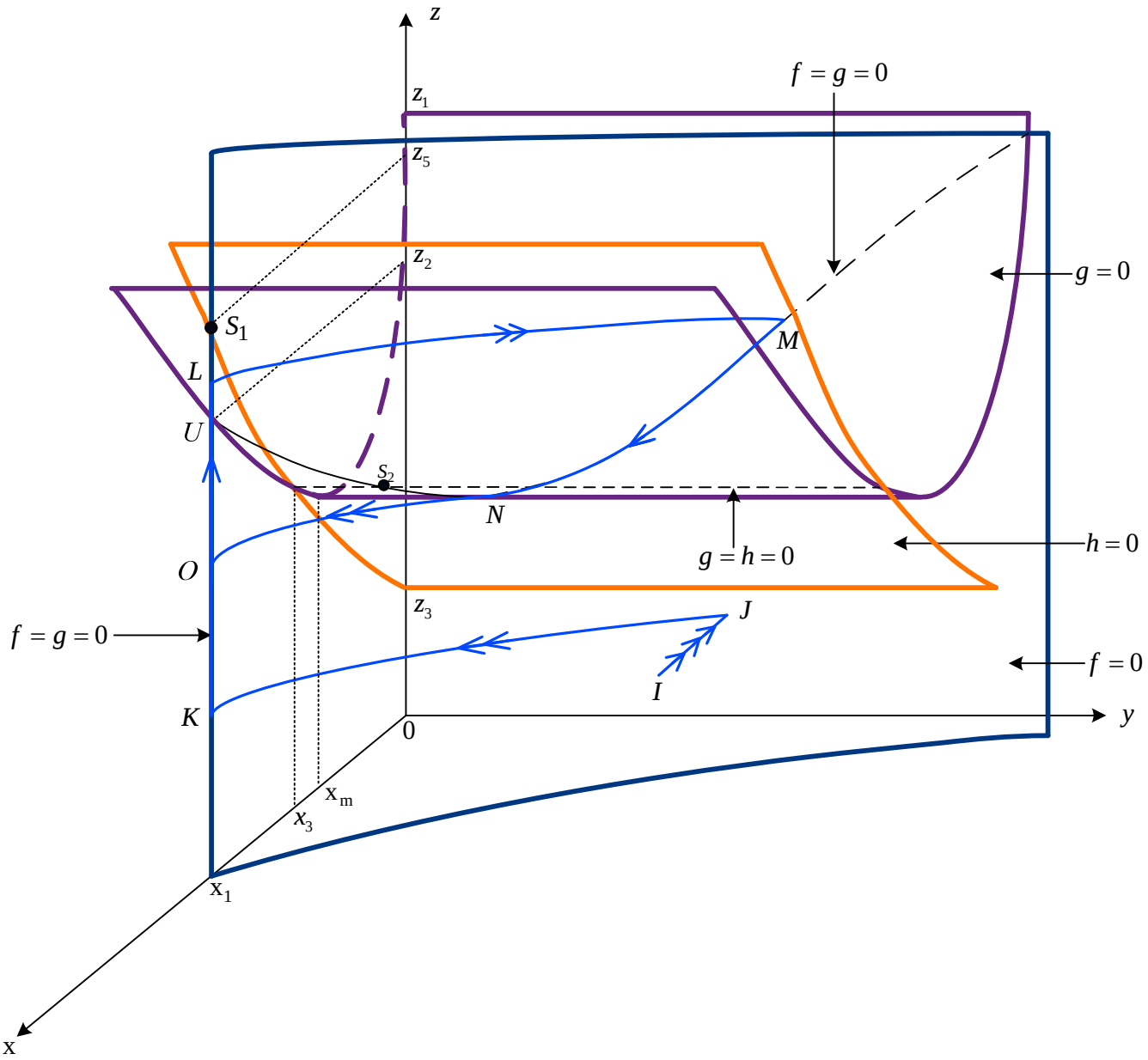


Fig. 1 The three equilibrium manifolds $\{f=0\},\{g=0\}$ and $\{h=0\}$ in the $(x,y,z)$ – space in the case of limit cycle exists. Segments of the trajectories with one, two, and three arrows represent slow, intermediate, and fast transitions, respectively.

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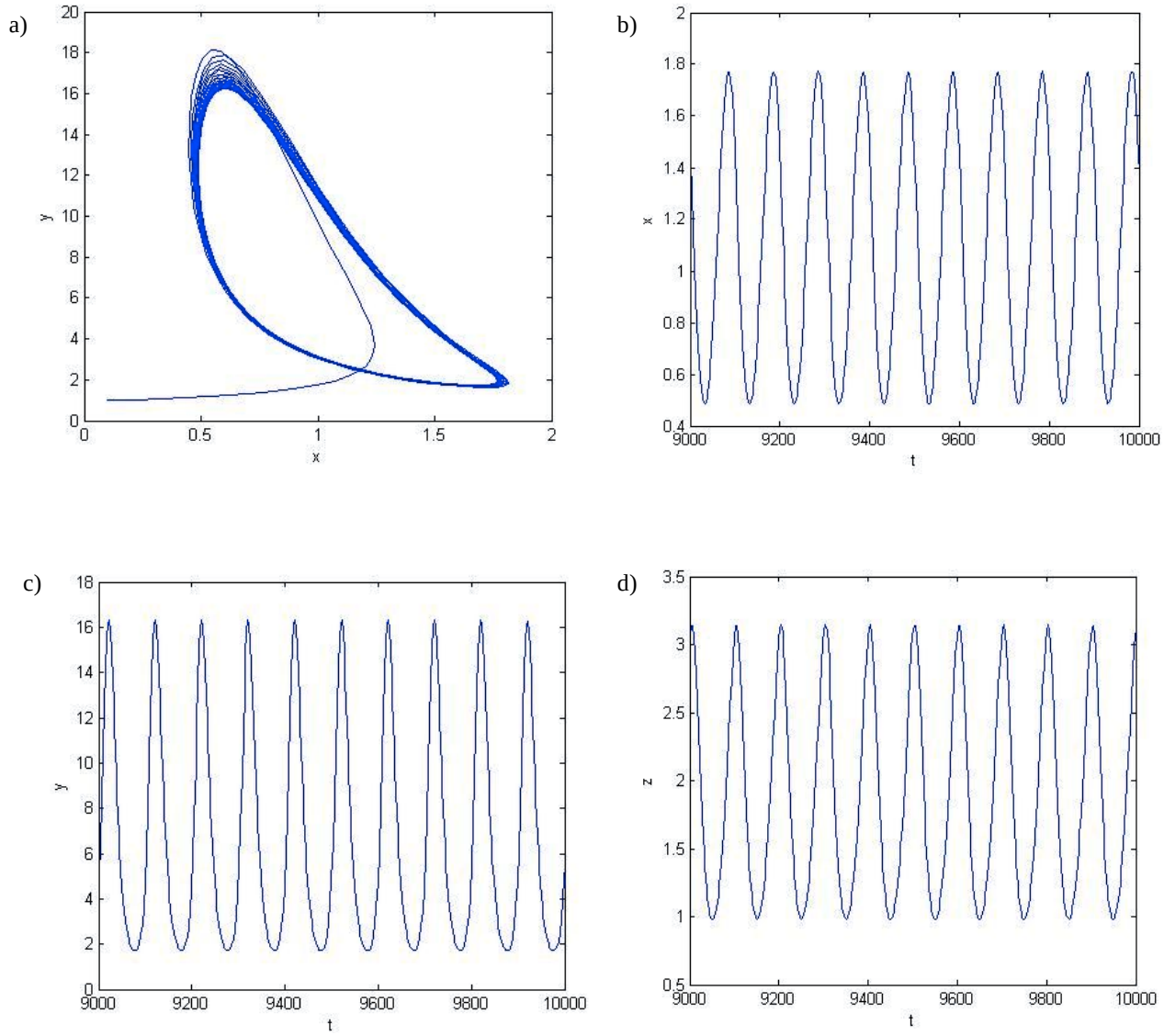


Fig. 2 A computer simulation of the model systems (4)-(6) with $c_1 = 0.7, c_2 = 0.3, c_3 = 0.5, c_4 = 0.1, c_5 = 0.7$, $k_1 = 2$, $k_2 = 5$, $k_3 = 2$, $d_1 = 0.1$, $d_2 = 0.25$, $d_3 = 0.3$, $\varepsilon = 0.45$, $\delta = 0.9$, $x(0) = 0.1$, $y(0) = 1$, and $z(0) = 5$. (a) The solution trajectory projected onto the ($x$,$y$)-plane. (b) The corresponding time courses of the level of serum vitamin D ($x$), (c) number of active osteoclastic cells ($y$), and (d) number of active osteoblastic cells ($z$).

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