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ORIGINAL ARTICLE

Mathematical Model for Two Germline Stem Cells Competing for Niche Occupancy

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Abstract In the *Drosophila* germline stem cell ovary niche, two stem cells compete with each other for niche occupancy to maintain stem cell quality by ensuring that differentiated stem cells are rapidly pushed out the niche and replenished by normal ones (Jin et al. in Cell Stem Cell 2:39–49, 2008). To gain a deeper understanding of this biological phenomenon, we have derived a mathematical model for explaining the physical interactions between two stem cells. The model is a system of two nonlinear first order and one second order differential equations coupled with E-cadherins expression levels. The model can explain the dynamics of the competition process of two germline stem cells and may help to reveal missing information obtained from experimental results. The model predicts several qualitative features in the competition process, which may help to design rational experiments for a better understanding of the stem cell competition process.

Keywords Germline stem cell competition · Stem cell niche

1 Introduction

Stem cells have the remarkable ability to undergo both self-renewal and differentiation (Xi and Xie 2005). Adult stem cells are responsible for generating new cells to replace lost cells in adult tissues due to natural cell turnover or injury. Age-dependent

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decrease in stem cell number or function can lead to age-dependent decline in tissue functions. Without adult stem cells or even reduced adult stem cell activities, a given tissue would not be able to maintain itself and then degenerate due to the limited lifespan of differentiated adult cells (Pan et al. 2007). On the other hand, adult stem cells keep self-renewing to maintain a stable population. Adult stem cells are known to reside in a special microenvironment, called the niche (Kirilly and Xie 2007), where they keep their identities and provide source cells for many types of differentiated cells. It is only in their niche that stem cells can function as stem cells. Although stem cells can bring a new hope for the treatment of many diseases such as Parkinson's, diabetes, and heart diseases, as well as injuries for which there has previously been no effective treatment (Clarke and Fuller 2006), uncontrolled stem cell growth or dysregulation of stem cells might lead to tumorigenesis, or other fatal diseases (Hombach-Klonisch et al. 2008). Understanding the mechanism of controlling stem cell behavior in its niche is crucial to the use of stem cells in regenerative medicine, as well as in understanding aging, tumor formation, and degenerative diseases (Reya et al. 2001).

A number of experimental studies have demonstrated the importance of interactions between stem cells and their niches in the control of self-renewal and differentiation. Most of these interactions are via signal transduction. The niche provides signaling molecules, and the signaling molecules activate membrane receptors of stem cells that in turn alters intracellular molecules within stem cells to create responses. These signals from niches strictly control stem cell's self-renewal and differentiation (Lin 2002; Li and Xie 2005). While none have investigated how stem cells within the same niche interact with one another, it has recently been shown that stem cells in the same niche interact with each other "physically" (Jin et al. 2008). In the process of competition, two stem cells interact with one another via "physical" interaction, both of them physically attach to their niche and physically push each other in competition for niche occupancy. The competitiveness is largely determined by the strength of the physical bonds between stem cells and their niches. This is a new mechanism of cell interaction: non-signaling interaction. The competition will lead to one germline stem cell forcing another out of the niche, ultimately resulting in one stem cell dominating the niche.

The discovery of this biological phenomenon is very important because it may reveal the mechanism of stem cell quality control which ensures that accidentally differentiated stem cells are rapidly removed from the niche and replaced by functional ones. It may also be related to the molecular mechanism of how stem cell population size is maintained and regulated. However, to understand the mechanism of how two germline stem cells compete with each other is challenging, since it involves physical interaction. It is confirmed that the germline stem cell competition is mediated by E-cadherins, a type of transmembrane proteins by which germline stem cells are anchored in their niche (Song et al. 2002), and that the intensity of E-cadherins appears to be important for germline stem cell competition, because a germline stem cell with more E-cadherin in the junction with its niche becomes more competitive than the one with lower E-cadherin levels. Thus, it is important to find out the quantitative relationship between the competitiveness and the E-cadherin intensity on the surface of a germline stem cell. An integrative modeling study will be helpful for quantitatively understanding the competitive relationship between adult stem cells.

In this article, we present a mathematical model for two germline stem cell competition which provides a first approximation of the physical interaction between stem cells. Since the competition between two germline stem cells does not require BMP signaling and dMys function, we will not consider signaling interaction in mathematical models. There are two key points in modeling germline stem cell competition for niche space. First, instead of considering competition for niche space directly, we model the competition for E-cadherins between germline stem cells and their niche. E-cadherins can adhere together only when they match each other. The intensity of E-cadherins is closely related to the contact area between a germline stem cell and its niche. One model is proposed for this adhesion process. Second, germline stem cells are approximately assumed to be as an elastic material, particularly, as springs. In this study, we use two spring system coupled with the adhesion process to model the germline stem cell competition. The model can describe the dynamics of the competition process which can explain and recover some missing information in discrete experimental results. The model predicts several qualitative features of the competition process, particularly it predicts that even for two germline stem cells with the same carrying level of E-cadherins there still is a case of one stem cell pushing the other one out of their niche when the E-cadherin level passes a bifurcation value.

The paper is organized as follows. In Sect. 2, the biological model is explained. In Sect. 3, our mathematical models are derived. In Sect. 4, we present some biological justification and numerical simulations of our models. In Sect. 5, we conduct mathematical analysis of the model to confirm numerical results. In Sect. 6, we draw conclusions, and discuss several aspects of our models and the challenges in modeling of two stem cell competition.

2 Biological Model

The study of mechanisms which govern stem cell behaviors is of significant importance. One of the major obstacles in stem cell research is to accurately identify stem cells in their native tissue environment due to their rarity and lack of unique molecular marker. In contrast, the *Drosophila* ovary offers unique advantages for studying molecular and genetic networks controlling stem cells because stem cells and the niche in the *Drosophila* ovary are easy to identify. The female *Drosophila* germline stem cell niche is identified at the tip of the germarium. Each female *Drosophila* has a pair of ovaries, which is composed of 12 to 16 ovarioles (Kirilly and Xie 2007). Each ovariole is a simple tubular structure known as the germarium. The most apical cells in the germarium are a row of 8 to 10 terminal filament cells. Next to the terminal filament cells, five to seven somatic cap cells form a germline stem cell niche. Two or three germline stem cells can be reliably identified by their location and size. Germline stem cells are anchored directly to the cap cells through E-cadherin-mediated cell adhesion, and they are the largest germ cells at the tip of the germarium; see Fig. 1.

E-cadherin is a type of transmembrane proteins. They play important roles in cell adhesion, ensuring that cells within tissues are bond together. The current view about E-cadherin mediated adhesion is that E-cadherins first associate with each other on

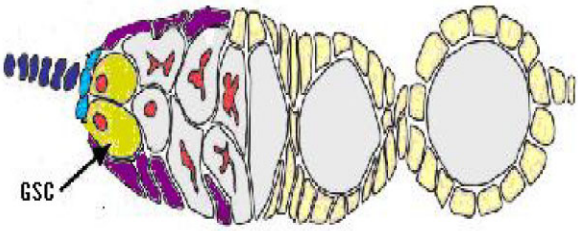

Fig. 1 A schematic diagram showing the germline stem cell niche at the tip of the germarium. *The big yellow cells* are germline stem cells. *The blue cells* are cap cells, and they attach each other to form the niche

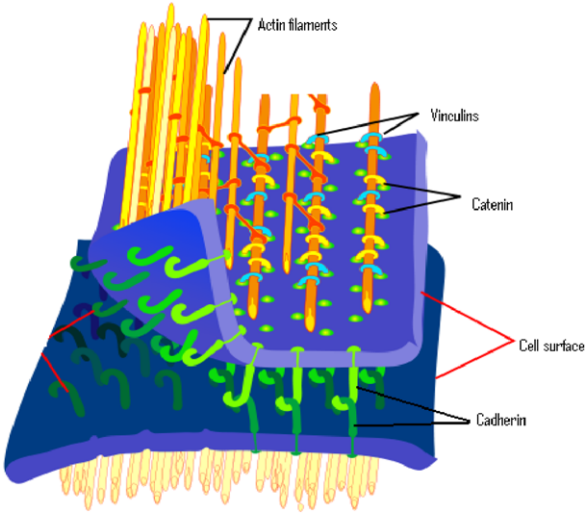

Fig. 2 A schematic diagram showing a germline stem cell attach to its niche through E-cadherin-mediated cell adhesion

the same cell surface to form *cis* dimers. The dimers on one cell surface then adhere to dimers on adjacent cells to form *trans* adhesive bonds (Leckband and Prakasam 2006). The E-cadherins on the surface of a germline stem cell can form adhesive bonds with E-cadherins on the surface of a cap call (niche cell), but can not form adhesive bonds with E-cadherins on the surface of other germline stem cell. Bonds of E-cadherins may have different lengths. When one bond is formed and it becomes short, its neighborhood E-cadherins can form more bonds. Thus, the bonding process may serve as a driving force to extend the contact area between a germline stem cell and its niche. Figure 2 shows how the bonding process to extend the contact area between a stem cell and its niche.

The self-renewal of germline stem cells is mainly controlled by bone morphogenetic proteins (BMP) and PIWI gene mediated signals from the niche cells (cap cells) (Cox et al. 2000). Bone morphogenetic proteins is a family of growth factors influencing bone and tissue growth within animals. PIWI gene encodes regulatory proteins which are responsible for maintaining incomplete differentiation in stem cells and maintaining the stability of cell division rates in germline cells. These signals from niche cells maintain germline stem cells by suppressing the expression of a differentiation-promoting gene, *bag of marbles* (*bam*) (Song et al. 2004), while the differentiation of germline stem cells requires *bam* and *bgcn* (*benign go-*

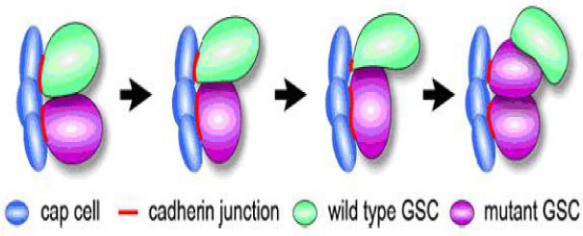

Fig. 3 A biological model explaining *bam*/*bgcn*-mediated germline stem cell competition. Initially, the *bam*/*bgcn* mutant germline stem cell (*purple*) has almost the same contact area with the niche (*blue*, cap cells) as the wild-type germline stem cell (*green*) does with the niche, and both have almost the same amount E-cadherin between them and the niche (*red*, E-cadherin). Over time, the mutant germline stem cell expands its contact area with the niche, and more E-cadherin accumulates in between the mutant germline stem cell and the niche. Eventually, the mutant germline stem cell pushes the wild-type germline stem cell to a minimum position, until the wild-type germline stem cell is pushed out the niche

nial cell neoplasm) (McKearin and Ohlstein 1995). The *bgcn* is *Drosophila* cystoblast differentiation factor (Szakmary et al. 2005). In Jin et al. (2008), the authors used loss-of-function and gain-of-function experiments to have showed that the differentiation-defective *bam* and *bgcn* mutant germline stem cells outcompete wild-type germline stem cells for niche occupancy. They further proved that this competition is not through inducing differentiation and apoptosis of wild-type germline stem cells. While the *bam* and *bgcn* mediated germline stem cell competition requires E-cadherins, different levels of E-cadherin expression in germline stem cells in the same niche can stimulate stem cell competition. It seems that the *bam* and *bgcn* mutant germline stem cells express higher levels of E-cadherin in the stem cell-niche junction and, thus, have a higher affinity with niche cells (cap cells). These experimental results suggest a novel mechanism of cell interaction: the *bam* and *bgcn* mutant stem cells do not promote apoptosis or differentiation of their wild-type counterparts in the same niche, instead they push their wild-type counterparts out of the niche through their adhesive advantage. A biological model for two germline stem cell competition was proposed as in Fig. 3.

3 Mathematical Model

As explained in Sect. 2, we assume that E-cadherins on the surface of a germline stem cell produce an attractive force between the germline stem cell and its niche (cap cells) within a certain distance (Geisbrecht and Montell 2002). We also assume germline stem cells are elastic material, and they can be deformed by external forces (Mofrad and Kamm 2006). For simplicity, we assume that a germline stem cell behaves like a spring (Evans and Calderwood 2007). The attractive force between the stem cell surface and the niche will increase the contact area between the stem cell and its niche by elongating or extending the stem cell. Although there are several methods or models for general cell adhesions (Leckband and Prakasam 2006), for example, biophysics method was applied in several studies (Armstrong et al. 2006; Bell 1978; Hammer and Lauffenburger 1987; Shapiro et al. 1995), none of them have

considered the E-cadherin intensity at cell level. For our purpose of modeling two germline stem cell competition, we will develop a simple model for cell adhesion.

Since E-cadherins between two cell membranes have to match each other in order to adhere, the E-cadherins in a germline stem cell surface only can match the E-cadherins in its niche (cap cell surfaces). Thus, we only consider the intensity of E-cadherins on the surfaces of germline stem cells. The intensity of E-cadherin between a germline stem cell and its niche will determines the contact area between the germline stem cell and its niche, and somehow determines the competitive ability of this stem cell. We will show experimental justification about this point in next section.

For simplicity, we consider the niche is in a plane with finite area, and germline stem cells can move or be extended in one dimensional space. Let $C(t)$ represent the intensity of E-cadherins on the surface of a given germline stem cell forming bonds with its niche, $x(t)$ represent the deformation of a given germline stem cell. For a given germline stem cell, there will be a maximum intensity of E-cadherin on its surface. This maximum intensity is determined by its biological property. We will call it *the carrying level*. (Notice that the term "intensity" is actually the word "amount" in this article.) If there is only one germline stem cell in the niche, it will start to contact the niche, and gradually "totally" attach to the niche. Here, "totally attach" means the contact area between this germline stem cell and the niche reaches the maximum, and the intensity of its E-cadherins also reaches its carrying level. To describe the dynamics, we consider the intensity of E-cadherins follows a logistic process when there is only one germline stem cell in the niche. As we assume, the germline stem cell behaves like a Hook's spring within a small deformation. If it is extended in one direction by x, by Hook's law, there will be a force which is equal to $-sx$, and this force will make the germline stem cell compressed, where s is the Young's modulus coefficient (Mofrad and Kamm 2006). Therefore, by Newton's second law, we have the following equations to describe the dynamics of the adhesion process.

$$\frac{dC(t)}{dt} = r(b)C(t)\frac{K(b) - C(t)}{K(b)}, \tag{1}$$

$$m\frac{d^2x(t)}{dt} = -sx(t) + \alpha C(t). \tag{2}$$

Here, $r(b)$ is the per capita increasing rate of E-cadherins, $K(b)$ is the carrying level of E-cadherins on the surface of the germline stem cell. The parameter (b) is determined by the biological property of the germline stem cell, particularly, by the gene *bam*/*bgcn*. The carrying level of E-cadherins of a germline stem cell is also determined by its intrinsic biology, particularly, *bam*/*bgcn* expression. m is the mass of the germline stem cell. The parameter α is the phenomenological coefficient which measures how much E-cadherins are converted to deriving force.

In general, an ovary niche has two or three germline stem cells. The modeling of the competition among three germline stem cells in one niche will be extremely difficult. We here only consider the competition between two germline stem cells in one niche.

When a niche has two germline stem cells, each of them has a trend to extend its contact area with the niche because of the adhesion process. Since the niche area is

limited, there will be a competition for the contact area with the niche (occupancy) between two germline stem cells. Alternatively, there will be a competition for "the common resource", E-cadherins in the niche (on the surfaces of cap cells), by matching E-cadherins on each surface of two germline stem cells. If we only consider this competition process, we could adopt the standard competition model in population dynamics.

Suppose the cell 1 is the differentiation-defective *bam/bgcn* mutant germline stem cell with upregulated E-cadherins, the cell 2 is the wild-type germline stem cell. Denote the intensity of E-cadherins of the stem cell 1 by $C_1(t)$, the intensity of E-cadherins of the stem cell 2 by $C_2(t)$. Then standard competition model gives the following system:

$$\frac{dC_1(t)}{dt} = r_1(b)C_1(t)\frac{K_1(b) - C_1(t)}{K_1(b)} - \frac{r_1(b)\beta_{12}(x)}{K_1(b)}C_1(t)C_2(t),$$
$$\frac{dC_2(t)}{dt} = r_2(b)C_2(t)\frac{K_2(b) - C_2(t)}{K_2(b)} - \frac{r_2(b)\beta_{21}(x)}{K_2(b)}C_1(t)C_2(t),$$

where parameters $r_i(b)$, $K_i(b)$ have similar meaning as in (1)–(2), $i = 1, 2$. The terms $\frac{r_1(b)\beta_{12}(x)}{K_1(b)}C_1(t)C_2(t)$ and $\frac{r_2(b)\beta_{21}(x)}{K_2(b)}C_1(t)C_2(t)$ represent competition between the cell 1 and the cell 2. If x is a constant, $\beta_{12}(x)$ and $\beta_{21}(x)$ both are constants, and they may not be the same. $\beta_{12}(x)C_2$ can be thought of as the contribution made by the cell 2 to a "decline in the increasing rate of E-cadherin" of the cell 1, and $\beta_{12}(x)$ is the per capita decline (caused by E-cadherin of the cell 2 on the cell 1). $\beta_{12}(x)$ measures the competitive effect of the cell 2 on the cell 1. Since $\beta_{12}(x)$ is a function of the niche space (or cell deformation) x, we implicitly include the competition for the niche space. Hence, an appropriate form of $\beta_{12}(x)$ will be given. $\beta_{21}(x)$ has a similar interpretation.

Meanwhile, during the competition of two germline stem cells, the contact area between a germline stem cell and the niche and thereby the size of a germline stem cell, will also be changed. For simplicity, we assume that the physical interaction between two germline stem cells is restricted in a plane (represented by a point) and it moves in the straight line because of two cells pushing each other. We use x to represent the fighting plane moving away from the position where there is no cell deformation. Since we assume a germline stem cell can be treated as a spring when there is small deformation by an external force, two germline stem cells pushing each other can be described by the two spring system.

Suppose the cell 1 is in the left of the origin of the x-axis and the cell 2 is in the right of the origin, and these two cells are in the x-axis. When $x = 0$, there is no deformation of cells. As a first approximation, we assume the external force is proportional to the intensity difference of E-cadherin between two germline stem cells. Then we have the following equation to represent the interaction of these two germline stem cells:

$$m\frac{d^2x(t)}{dt^2} = -s_1(b)x(t) - s_2(b)x(t) + \alpha\big(C_1(t) - C_2(t)\big),$$

where $s_i(b)$ is the Young's modulus coefficient of the cell i, $i = 1, 2$.

Thus, we get the model equations, two first-order differential equations and one second-order differential equations. They are all nonlinear, and coupled to each other. The initial position is $x = 0$ where the two stem cells have no deformation and they just attach to each other. The initial E-cadherin levels for the two stem cells can be chosen differently.

$$\frac{dC_1(t)}{dt} = r_1(b)C_1(t)\frac{K_1(b) - C_1(t)}{K_1(b)} - \frac{r_1(b)\beta_{12}(x)}{K_1(b)}C_1(t)C_2(t), \tag{3}$$

$$\frac{dC_2(t)}{dt} = r_2(b)C_2(t)\frac{K_2(b) - C_2(t)}{K_2(b)} - \frac{r_2(b)\beta_{21}(x)}{K_2(b)}C_1(t)C_2(t), \tag{4}$$

$$m\frac{d^2x(t)}{dt^2} = -s_1(b)x(t) - s_2(b)x(t) + \alpha\big(C_1(t) - C_2(t)\big). \tag{5}$$

If we skip the parameters b (*bam/bgcn*) and the space x, this is a well-studied Lotka–Volterra model for the competition of two species at the population level. However, we model the competition for the space between two individual cells. The introduction of functions $\beta_{12}(x)$ and $\beta_{21}(x)$ and space equation of the spring system changes the model from the population level of E-cadherins to the individual level of cells. We need two specific forms of functions $\beta_{12}(x)$ and $\beta_{21}(x)$. They could be estimated from experimental data. In our study, we choose these two functions to be linear functions of cell deformation as a first approximation.

$$\beta_{12}(x) = \frac{l - x}{2l}, \qquad \beta_{21}(x) = \frac{l + x}{2l}, \tag{6}$$

where l is the maximum of extension or deformation of germline stem cells.

4 Model Justification and Numerical Simulations

The experiments we have conducted were described in Jin et al. (2008). Adult female *Drosophila* were cultured. The Flp-mediated mitotic recombination technique was used to generate mutant germline stem cell clones. Ovaries were dissected from some of the females after 1, 2, and 3 weeks. The measurements of the contact area between the germline stem cell and its niche, measurements of intensity of E-cadherins between the germline stem cell and its niche were taken. A typical data set is shown in Fig. 4.

From these data, the maximum ratio of the contact area between the germline stem cell 1 and its niche to the contact area between the germline stem cell 2 and its niche is 5.45, while the minimum ratio is 0.63, and the average is 1.8. The maximum ratio of the intensity between the germline stem cell 1 and its niche to the intensity between germline stem cell 2 and its niche is 10.89, while the minimum ratio is 0.56, and the average is 2.31. There is a rough correlation between the contact area and the intensity of a germline stem cell. It seems apparent that some wild-type germline stem cell is pushed out of its niche, while in a different niche the wild-type germline stem cell even pushes its mutant counterpart back. Therefore, an oscillation of the interaction between the germline stem cell and its mutant counterpart seems to be a

Clones	Area		Area ratio	Cadherin intensity		Intensity ratio
	LacZ-positve-clone	LacZ-negetive -clone	LacZ- vs LacZ+	LacZ-positve-clone	LacZ-negetive -clone	LacZ- vs LacZ+
bam-001	23.00900078	125.2850037	5.45	769471	8378833	10.89
bam-010	9.251000404	31.30900002	3.38	199646	1037321	5.20
bam-009	7.504000187	23.93600082	3.19	401486	1847424	4.60
bam-006	48.55500031	110.2480011	2.27	1864592	5088920	2.73
bam-015	29.46500015	58.61500168	1.99	778066	1551986	1.99
bam-007	11.39099979	22.13100052	1.94	435752	967813	2.22
bam-022	70.27999878	117.8909988	1.68	5005139	6945037	1.39
bam-012	75.67500305	121.6220016	1.61	3909388	5913809	1.51
bam-003	44.10900116	88.18699646	2.00	1886809	3724403	1.97
bam-018	52.97900009	80.00099945	1.51	2517391	3949620	1.57
bam-019	56.2820015	83.41100311	1.48	3679092	6629402	1.80
bam-013	84.73400116	124.2850037	1.47	3820042	6852591	1.79
bam-016	57.7820015	81.08799744	1.40	3577654	5438817	1.52
bam-017	50.86299896	67.9280014	1.34	2469154	4661610	1.89
bam-011	44.6780014	47.31900024	1.06	2544294	2250546	0.88
bam-002	32.48899841	31.04899979	0.96	1134017	1416003	1.25
bam-008	27.07999992	25.4640007	0.94	1277021	898968	0.70
bam-020	89.54000092	75.9469986	0.85	4271531	3538942	0.83
bam-023	80.67900085	68.23400116	0.85	4414240	4078026	0.92
bam-005	28.83300018	18.04000092	0.63	1001277	561261	0.56
Average	46.26	70.10	1.80	2297803.10	3786566.60	2.31

Fig. 4 A set of data about contact areas, E-cadherin intensities of *bam* mutant germline stem cells and their niches, and that of wild-type germline stem cells and their niches. These data were measured at week 3

very plausible explanatory mechanism. The average numbers may be not very significant since they were taken from 20 different niches. This set of data was measured at week 3. The other data which were measured at week 1, week 2, week 4, and longer (not showing here) have the similar pattern. These experimental results suggest that each pair of germline stem cells in one niche may have its own dynamics, particularly may have its own time scale. In Sect. 3, we present niche-based simplified models in order to catch the basic dynamics of one germline stem cell adhesion to its niche and the competition of two germline stem cells in the same niche. Instead of fitting the data at the average, we are interested in describing and predicting the dynamic process of competition between two germline stem cells. We will numerically solve the models, and present some representative numerical results to demonstrate the model predictions in the following. In the next section, we give mathematical analysis to confirm these numerical predictions.

The system (1)–(2) describes the dynamics of adhesion process when the niche has only one germline stem cell. Figure 5 shows the intensity of E-cadherins between the stem cell and its niche will reach the carrying level as the cell has the maximum deformation (extension). However, the germline stem cell will not stop to move and, instead, it will oscillate with a small amplitude around the maximum extension. We do not show the change of the intensity or the extension of the germline stem cell over time, since we are interested in the relation between the extension and intensity of the cell.

The system (3)–(5) describes the competition between two germline stem cells in the same niche. The model predicts there are two equilibrium solutions when one germline stem cell without E-cadherins for whatever parameter values are chosen. Figure 6 shows the dynamic relation between the intensity of E-cadherins and the

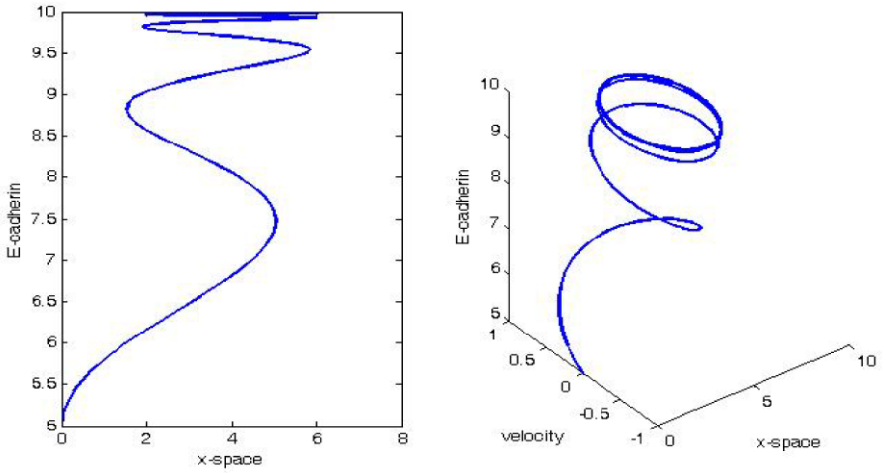

Fig. 5 *The left figure* shows the relation between the deformation of the germline stem cell and the intensity of E-cadherins. *The horizontal axis*, "x-axis," represents the deformation of the germline stem cell, while *the vertical axis* represents the intensity of E-cadherins. *The right figure* shows how the germline stem cell extends with E-cadherins in space. There is an extra dimension for the velocity of the germline stem cell. The system (1)–(2) was simulated when $r = 0.1$, $K = 10$, $s = 0.1$, $\alpha = 0.04$, and $m = 1$

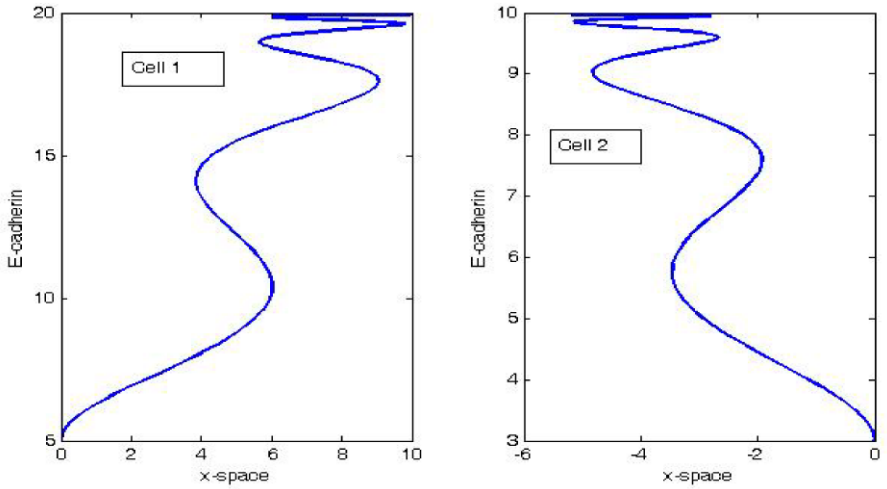

Fig. 6 *The left figure* shows the deformation of the cell 1 with E-cadherins, and the cell 1 is originally in the left of the origin of x-axis. *The right figure* shows the deformation of the cell 2 with E-cadherins, and the cell 2 is originally in the right of the origin of x-axis. The system (3)–(5) was simulated when $r_1 = 0.1$, $r_2 = 0.1$, $K_1 = 20$, $K_2 = 10$, $s_1 = 0.05$, $s_2 = 0.05$, $l = 10$, $\alpha = 0.04$, and $m = 1$

extension of each cells. This is similar to the dynamics shown in Fig. 5 except one cell serves as an extra spring.

When the two germline stem cells in the same niche have different carrying levels of E-cadherins on their surfaces, as one is mutant and the other is wild-type,

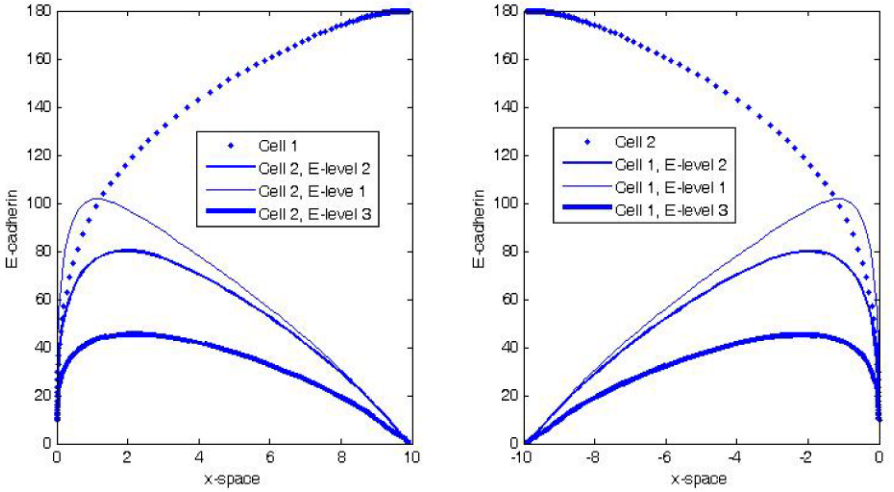

Fig. 7 *The left figure* shows the competition of two germline stem cells where the cell 1 is a winner. The cell 1 has the carrying level of E-cadherins above the carrying level of E-cadherins in the cell 2 for three cases. For illustrative purpose, fixed $K_1 = 180$ for the cell 1, the cell 2 has three different levels of E-cadherins: E-level 1 is $K_2 = 170$, E-level 2 is $K_2 = 150$, E-level 3 is $K_2 = 100$. *The right figure* shows the competition of two cells where the cell 2 is a winner. Similarly, fixed $K_2 = 180$ for the cell 2, the cell 1 has three different levels of E-cadherins: E-level 1 is $K_1 = 170$, E-level 2 is $K_1 = 150$, E-level 3 is $K_1 = 100$. For all these computations, other parameter values are the same: $r_1 = r_2 = 0.5$, $s_1 = s_2 = 0.5$, $l = 10$, $\alpha = 0.055$, and $m = 1$

the E-cadherin up-regulated cell will push the other out of their niche. Figure 7 shows several cases where one cell has a high E-cadherin carrying level which always pushes the other one out of their niche.

When the two germline cells in the same niche have the same carrying level of E-cadherins on their surfaces, the model predicts there is a threshold for the carrying level of E-cadherins. Below this threshold, two cells will reach equilibrium, and both stay in the niche. While above this threshold, one cell will push the other out of the niche. Actually, this threshold is a bifurcation value of the intensity of E-cadherins. Figure 8 shows when two germline stem cells "coexistence peacefully", and when one cell must get out of their niche.

5 Mathematical Analysis of the Models

5.1 Analysis of the Model for Adhesion Process

The system (1)–(2) can be treated as a three-dimensional system, where the third dimension is for the velocity of the cell extension during adhesion process. It has two equilibrium solutions, the trivial equilibrium $(0, 0, 0)$, and nontrivial equilibrium $(K, \frac{\alpha K}{s}, 0)$. At the trivial equilibrium point, the variational matrix has eigenvalues, r and $\pm i\sqrt{s}$. Hence, the trivial equilibrium is unstable. At the nontrivial equilibrium point, the variational matrix has eigenvalues, $-r$ and $\pm i\sqrt{s}$. So, the nontrivial equilibrium solution is locally stable, but not locally asymptotically stable. In

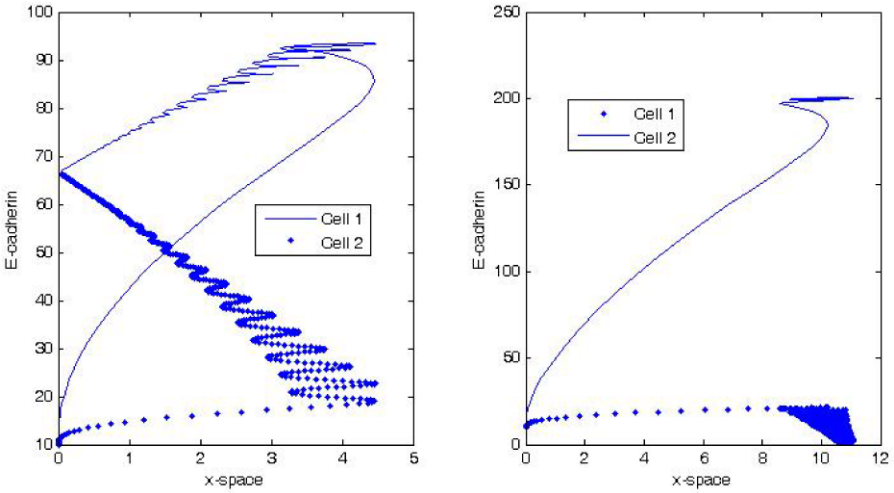

Fig. 8 *The left figure* shows intensities of E-cadherins of both germline stem cells reach equilibrium values, and they both reside in the niche when the carrying level of E-cadherins, $K_1 = K_2$, below the threshold. *The right figure* shows the intensity of E-cadherins of one cell reaches its carrying level, while the other decreases to a low level and eventually is pushed out when the carrying level of E-cadherins, $K_1 = K_2$, but above the threshold. *For the left figure*, $K_1 = K_2 = 100$, and *for the right figure*, $K_1 = K_2 = 200$. All other parameter values are the same: $r_1 = 0.8$, $r_2 = 0.2$, $s_1 = 0.7$, $s_2 = 0.4$, $l = 10$, $\alpha = 0.06$, and $m = 1$

fact, when the initial intensity of E-cadherins is c_0, which satisfies $0 \le c_0 \le K$, the solution to (1) is given by $C(t) = \frac{c_0 K e^{rt}}{K + c_0(e^{rt} - 1)}$ since the equation is a logistic equation. Given the initial position and the initial velocity x_0 and v_0 respectively, the equation $m\frac{d^2x}{dt^2} = -sx$ and $m\frac{d^2x}{dt^2} = -sx + \alpha K$ have solutions $x(t) = x_0 \cos\sqrt{\frac{s}{m}}t + \frac{v_0}{\sqrt{\frac{s}{m}}} \sin\sqrt{\frac{s}{m}}t$ and $x(t) = x_0 \cos\sqrt{\frac{s}{m}}t + \frac{v_0}{\sqrt{\frac{s}{m}}} \sin\sqrt{\frac{s}{m}}t + \frac{\alpha K}{ms}$, respectively. Since $-sx < -sx + \alpha C(t) < -sx + \alpha K$, by using comparison theorem, we have an estimation for the extension of the germline stem cell which is given in the following lemma.

Lemma 5.1 *For the initial values c_0, x_0 and $v_0 = x'(0)$, the solution of the system (1)–(2) satisfies*

$$x_0 \cos\sqrt{\frac{s}{m}}t + \frac{v_0}{\sqrt{\frac{s}{m}}} \sin\sqrt{\frac{s}{m}}t \le x(t) \le x_0 \cos\sqrt{\frac{s}{m}}t + \frac{v_0}{\sqrt{\frac{s}{m}}} \sin\sqrt{\frac{s}{m}}t + \frac{\alpha K}{ms},$$

$$C(t) = \frac{c_0 K e^{rt}}{K + c_0(e^{rt} - 1)}.$$

Therefore, any solution of the system (1)–(2) will approach the nontrivial equilibrium point or a periodic solution on the center manifold as t approaches the infinity. The center manifold is in the plane $C = K$. This is observed in Fig. 5.

5.2 Analysis of the Model for Two Germline Stem Cell Competition

The model for the competition of two germline stem cells (3)–(5) can be considered as a four-dimensional system, where the fourth dimension is for the velocity of the cell deformation. We will not non-dimensionalize the model since we would like to make the importance of some parameters apparent. The equilibrium solutions are

$$E_0 = (0, 0, 0, 0), \qquad E_1 = \left(K_1(b), 0, \frac{\alpha K_1(b)}{s_1 + s_2}, 0\right),$$
$$E_2 = \left(0, K_2(b), -\frac{\alpha K_2(b)}{s_1 + s_2}, 0\right),$$

and

$$\left(\frac{K_1(b) - \beta_{12}(\overline{x})K_2(b)}{1 - \beta_{12}(\overline{x})\beta_{21}(\overline{x})}, \quad \frac{K_2(b) - \beta_{21}(\overline{x})K_1(b)}{1 - \beta_{12}(\overline{x})\beta_{21}(\overline{x})}, \quad \overline{x}, \quad 0\right),$$

where $\overline{x}$ satisfies

$$\big(1 - \beta_{12}(x)\beta_{21}(x)\big)(s_1 + s_2)x - \alpha K_1(b)\big(1 + \beta_{21}(x)\big) + \alpha K_2(b)\big(1 + \beta_{12}(x)\big) = 0.$$

It is possible there are more equilibrium solutions.

For simplicity, we will drop the parameter b, and consider the related functions to be constants.

The variational matrix of the system (3)–(5) is given by

$$\begin{pmatrix} r_1 - \frac{r_1}{K_1}(2C_1 + \beta_{12}(x)C_2) & -\frac{r_1}{K_1}\beta_{12}(x)C_1 & -\frac{r_1}{K_1}\beta'_{12}(x)C_1C_2 & 0 \\ -\frac{r_2}{K_2}\beta_{21}(x)C_2 & r_2 - \frac{r_2}{K_2}(2C_2 + \beta_{21}(x)C_1) & -\frac{r_2}{K_2}\beta'_{21}(x)C_1C_2 & 0 \\ 0 & 0 & 0 & 1 \\ \frac{\alpha}{m} & -\frac{\alpha}{m} & -\frac{s_1}{m} - \frac{s_2}{m} & 0 \end{pmatrix}.$$

For the equilibrium points E_0, E_1, and E_2, one can easily obtain their stability by computing eigenvalues of the variational matrix.

The trivial equilibrium $E_0 = (0, 0, 0, 0)$ is unstable since the variational matrix at this point has at least two positive eigenvalues, r_1 and r_2.

For the equilibrium point $E_1 = (K_1, 0, \frac{\alpha K_1}{s_1+s_2}, 0)$, the variational matrix has eigenvalues: $-r_1$, $r_2(1 - \frac{K_1}{K_2}\frac{l(s_1+s_2)+\alpha K_1}{2l(s_1+s_2)})$, $i\sqrt{\frac{s_1+s_2}{m}}$, and $-i\sqrt{\frac{s_1+s_2}{m}}$. Hence, when $\frac{K_2}{K_1} < \frac{1}{2} + \frac{\alpha K_1}{2l(s_1+s_2)}$, this equilibrium point is locally stable. Since there is a pair of purely imaginary eigenvalues, it is not locally asymptotically stable, and it is possible the solutions close to this equilibrium point are oscillating around this equilibrium point.

For the equilibrium point $E_2 = (0, K_2, \frac{\alpha K_2}{s_1+s_2}, 0)$, the variational matrix has eigenvalues: $-r_2$, $r_2(1 - \frac{K_2}{K_1}\frac{l(s_1+s_2)-\alpha K_2}{2l(s_1+s_2)})$, $i\sqrt{\frac{s_1+s_2}{m}}$, and $-i\sqrt{\frac{s_1+s_2}{m}}$. S, when $\frac{K_1}{K_2} < \frac{1}{2} - \frac{\alpha K_2}{2l(s_1+s_2)}$, this equilibrium point is locally stable, but not locally asymptotically stable.

The Fig. 6 shows two cases of the stability at the equilibrium points E_1 and E_2. We observe that there are small oscillations around these equilibrium points in x-space, but the intensity of E-cadherins keep the same value. It is similar to the adhesion process.

When $\beta_{12}(x) = \frac{l-x}{2l}$ and $\beta_{21}(x) = \frac{l+x}{2l}$,

$$\big(1-\beta_{12}(x)\beta_{21}(x)\big)(s_1+s_2)x - \alpha K_1(b)\big(1+\beta_{21}(x)\big) + \alpha K_2(b)\big(1+\beta_{12}(x)\big) = 0$$

reduces to

$$(s_1+s_2)x^3 + \big(3sl^2 - 2\alpha l(K_1+K_2)\big)x + 6\alpha l^2(K_2-K_1) = 0. \tag{7}$$

Since there is a maximum extension (deformation) for a germline stem cell, denoted by l, we can assume that a germline stem cell will leave the niche when the deformation of its counterpart in the same niche exceeds the length l. The following Theorem 5.1 gives some conditions for one germline stem cell leaving its niche.

Theorem 5.1 *Given $K_2 < K_1$, if $2K_1 - K_2 \geq \frac{(s_1+s_2)l}{\alpha}$, or $2K_1 - K_2 < \frac{(s_1+s_2)l}{\alpha}$ and $5K_1 - K_2 > \frac{7(s_1+s_2)l}{\alpha}$, then the cell 1 will push the cell 2 out of their niche. Symmetrically, given $K_2 > K_1$, if $2K_2 - K_1 \geq \frac{(s_1+s_2)l}{\alpha}$, or $2K_2 - K_1 < \frac{(s_1+s_2)l}{\alpha}$ and $5K_2 - K_1 > \frac{7(s_1+s_2)l}{\alpha}$, then the cell 2 will push the cell 1 out of their niche.*

Proof Denote $f(x) = (s_1+s_2)x^3 + (3(s_1+s_2)l^2 - 2\alpha l(K_1+K_2))x + 6\alpha l^2(K_2 - K_1)$. When $K_2 < K_1$, one has $f(0) < 0$. Since $(s_1+s_2) > 0$, there must be a positive number at which $f(x)$ is positive. Then from the intermediate value theorem, there exists a positive number at which $f(x)$ takes zero. Hence, (7) has at least one positive root.

If $f(l) \leq 0$, then there exists a root $\bar{x}$ of (7), and $\bar{x} \geq l$. The system (3)–(5) has the equilibrium point $(\frac{K_1-\beta_{12}(\bar{x})K_2}{1-\beta_{12}(\bar{x})\beta_{21}(\bar{x})}, \frac{K_2-\beta_{21}(\bar{x})K_1}{1-\beta_{12}(\bar{x})\beta_{21}(\bar{x})}, \bar{x}, 0)$. When the system approaches this equilibrium point, the cell 1 will reach its maximum extension, and the cell 2 will be compressed and has to leave its niche. From the condition $f(l) \leq 0$, we have $f(l) = 4(s_1+s_2)l^3 - 8\alpha l^2 K_1 + 4\alpha l^2 K_2 \leq 0$. Furthermore, $(s_1+s_2)l - 2\alpha K_1 + \alpha K_2 \leq 0$. Hence, $\frac{(s_1+s_2)l}{\alpha} \leq 2K_1 - K_2$. It is easy to see that the condition $\frac{(s_1+s_2)l}{\alpha} \leq 2K_1 - K_2$ means $f(l) \leq 0$.

If $f(l) > 0$ and $f(2l) < 0$, then $f(x)$ has a zero between l and $2l$. A similar argument gives the conclusion. While from the $f(l) > 0$, one easily gets $2K_1 - K_2 < \frac{(s_1+s_2)l}{\alpha}$. From $f(2l) < 0$, one has $f(2l) = 8(s_1+s_2)l^3 + 2l(3(s_1+s_2)l^2 - 2\alpha l(K_1+K_2)) + 6\alpha l^2(K_2-K_1) < 0$. That is, $7(s_1+s_2)l - \alpha(5K_1 - K_2) < 0$. Hence, $5K_1 - K_2 > \frac{7(s_1+s_2)l}{\alpha}$.

Similarly, one can get the proof for the case $K_2 > K_1$. □

This theorem confirms the observation in Fig. 7. Most importantly, it confirms the experimental results in Jin et al. (2008), also mentioned in Sect. 2.

Consider the case when $K_2 = K_1$, (7) has the root $x = 0$, and other possible two roots $x = \pm\sqrt{\frac{2\alpha l(K_1+K_2)}{s_1+s_2} - 3l^2}$ if $\frac{2\alpha l(K_1+K_2)}{s_1+s_2} - 3l^2 > 0$. When $x = 0$, the third equilibrium solution is $(\frac{2}{3}K, \frac{2}{3}K, 0, 0)$, where $K_2 = K_1 = K$. The variational matrix at

this point is given by

$$\begin{pmatrix} -\frac{2}{3}r_1 & -\frac{1}{3}r_1 & \frac{2r_1K}{9l} & 0 \\ -\frac{1}{3}r_2 & -\frac{2}{3}r_2 & -\frac{2r_2K}{9l} & 0 \\ 0 & 0 & 0 & 1 \\ \frac{\alpha}{m} & -\frac{\alpha}{m} & -\frac{s_1+s_2}{m} & 0 \end{pmatrix}.$$

The characteristic polynomial is given by

$$\lambda^4 + \frac{2(r_1+r_2)}{3}\lambda^3 + \frac{3(s_1+s_2)+r_1r_2m}{3m}\lambda^3 + \frac{2(r_1+r_2)(3(s_1+s_2)l-\alpha K)}{9ml}\lambda + \frac{r_1r_2(3(s_1+s_2)l-4\alpha K)}{9ml} = 0. \tag{8}$$

Theorem 5.2 *Suppose* $K_1 = K_2 = K$, *at* $K = \frac{3(s_1+s_2)l}{4\alpha}$, *the system* (3)–(5) *has a supercritical pitchfork bifurcation. When* $K < \frac{3(s_1+s_2)l}{4\alpha}$, *the system has the fourth equilibrium point* $E_3 = (\frac{2}{3}K, \frac{2}{3}K, 0, 0)$ *which is locally asymptotically stable. When* $K > \frac{3(s_1+s_2)l}{4\alpha}$, *the system has two more equilibrium points* $E_4 = (\frac{2l(l+\bar{x}_1)}{3l^2+\bar{x}_1^2}K, \frac{2l(l-\bar{x}_1)}{3l^2+\bar{x}_1^2}K, \bar{x}_1, 0)$, $E_5 = (\frac{2l(l+\bar{x}_2)}{3l^2+\bar{x}_2^2}K, \frac{2l(l-\bar{x}_2)}{3l^2+\bar{x}_2^2}K, \bar{x}_2, 0)$ *where* $\bar{x}_1 = \sqrt{\frac{4alK}{s} - 3l^2}$ *and* $\bar{x}_2 = -\sqrt{\frac{4alK}{s} - 3l^2}$, *and* E_3 *is unstable.*

Proof Given $K_1 = K_2 = K$. When $K \le \frac{3(s_1+s_2)l}{4\alpha}$, (7) has only one real root, 0. When $K > \frac{3(s_1+s_2)l}{4\alpha}$, (7) has three real roots, 0 and $x = \pm\sqrt{\frac{4alK}{s} - 3l^2}$. Correspondingly, the system (3)–(5) has the fourth equilibrium point $E_3 = (\frac{2}{3}K, \frac{2}{3}K, 0, 0)$ when $K \le \frac{3(s_1+s_2)l}{4\alpha}$. When $K > \frac{3(s_1+s_2)l}{4\alpha}$, the system has fifth and sixth equilibrium points, $E_4 = (\frac{2l(l+\bar{x}_1)}{3l^2+\bar{x}_1^2}K, \frac{2l(l-\bar{x}_1)}{3l^2+\bar{x}_1^2}K, \bar{x}_1, 0)$, $E_5 = (\frac{2l(l+\bar{x}_2)}{3l^2+\bar{x}_2^2}K, \frac{2l(l-\bar{x}_2)}{3l^2+\bar{x}_2^2}K, \bar{x}_2, 0)$ where $\bar{x}_1 = \sqrt{\frac{4alK}{s} - 3l^2}$ and $\bar{x}_2 = -\sqrt{\frac{4alK}{s} - 3l^2}$. A supercritical pitchfork bifurcation occurs at $K = \frac{3(s_1+s_2)l}{4\alpha}$.

Now we verify the stability of the equilibrium point E_3. If all eigenvalues of the variational matrix at this point have negative real part, then it is locally asymptotically stable. We check this by using the Routh–Hurwitz criteria.

$$H_1 = \left(\frac{2(r_1+r_2)}{3}\right),$$

this is a positive number.

$$H_2 = \begin{pmatrix} \frac{2(r_1+r_2)}{3} & 1 \\ \frac{2(r_1+r_2)(3(s_1+s_2)l-\alpha K)}{9ml} & \frac{3(s_1+s_2)+r_1r_2m}{3m} \end{pmatrix},$$

and $\det(H_2) = \frac{2(r_1+r_2)(lr_1r_2m+\alpha K)}{9ml} > 0$.

$$H_3 = \begin{pmatrix} \frac{2(r_1+r_2)}{3} & 1 & 0 \\ \frac{2(r_1+r_2)(3(s_1+s_2)l-\alpha K)}{9ml} & \frac{3(s_1+s_2)+r_1r_2m}{3m} & \frac{2(r_1+r_2)}{3} \\ 0 & \frac{r_1r_2(3(s_1+s_2)l-4\alpha K)}{9ml} & \frac{2(r_1+r_2)(3(s_1+s_2)l-\alpha K)}{9ml} \end{pmatrix},$$

and $\det(H_3) = \frac{4\alpha K}{81m^2l^2}(r_1+r_2)^2(3lr_1r_2m + 3(s_1+s_2)l - \alpha K)$. When $K < \frac{3(s_1+s_2)l}{4\alpha}$, $\det(H_3) > 0$.

$$H_4 = \begin{pmatrix} \frac{2(r_1+r_2)}{3} & 1 & & \\ \frac{2(r_1+r_2)(3(s_1+s_2)l-\alpha K)}{9ml} & \frac{3(s_1+s_2)+r_1r_2m}{3m} & & \\ 0 & \frac{r_1r_2(3(s_1+s_2)l-4\alpha K)}{9ml} & & \\ 0 & 0 & & \\ & & 0 & 0 \\ & & \frac{2(r_1+r_2)}{3} & 1 \\ & & \frac{2(r_1+r_2)(3(s_1+s_2)l-\alpha K)}{9ml} & \frac{3(s_1+s_2)+r_1r_2m}{3m} \\ & & 0 & \frac{r_1r_2(3(s_1+s_2)l-4\alpha K)}{9ml} \end{pmatrix}$$

and $\det(H_4) = \det(H_3)\frac{r_1r_2(3(s_1+s_2)l-4\alpha K)}{9ml}$. When $K < \frac{3(s_1+s_2)l}{4\alpha}$, $\det(H_4) > 0$.

Hence, the equilibrium solution $(\frac{2}{3}K, \frac{2}{3}K, 0, 0)$ is locally asymptotically stable if $K < \frac{3(s_1+s_2)l}{4\alpha}$. If $K > \frac{3(s_1+s_2)l}{4\alpha}$, then $\det(H_4)$ or $\det(H_3)$ is negative. So, E_3 is unstable. □

As mentioned above, if the deformation of one germline stem cell exceeds its maximum extension, the other germline stem cell will be pushed out of the niche. If $K > \frac{(s_1+s_2)l}{\alpha}$, of course, $K > \frac{3(s_1+s_2)l}{4\alpha}$, (7) has roots, $x = \pm\sqrt{\frac{4alK}{s} - 3l^2}$. Since $\frac{4alK}{s} - 3l^2 = (\frac{4\alpha K}{sl} - 3)l^2 > l^2$, one root $\bar{x}_1$ is greater than l, and the other root $\bar{x}_2$ is smaller than $-l$. The system (3)–(5) have equilibrium points $(\frac{2l(l+\bar{x}_1)}{3l^2+\bar{x}_1^2}K, \frac{2l(l-\bar{x}_1)}{3l^2+\bar{x}_1^2}K, \bar{x}_1, 0)$ and $(\frac{2l(l+\bar{x}_2)}{3l^2+\bar{x}_2^2}K, \frac{2l(l-\bar{x}_2)}{3l^2+\bar{x}_2^2}K, \bar{x}_2, 0)$. Both of them are out of the range of the germline stem cell extension, therefore, there is a chance one cell leave its niche. We write this point as a corollary.

Corollary 5.1 *When $K_1 = K_2 = K$ and $K > \frac{(s_1+s_2)l}{\alpha}$, there are equilibrium points whose $x-$ components are greater than l or smaller than $-l$. In other words, there is a chance that one cell will leave its niche.*

Figure 8 shows two cases of the model behaviors when both germline stem cells have the same carrying levels of E-cadherins. One case shows two germline stem cells coexist, and the other shows one stem cell is pushed out.

We summarize some analytical results in Fig. 9. Since we are mostly interested in the intensity of E-cadherins in this study, all other parameters are held as constants when the results were produced in this picture.

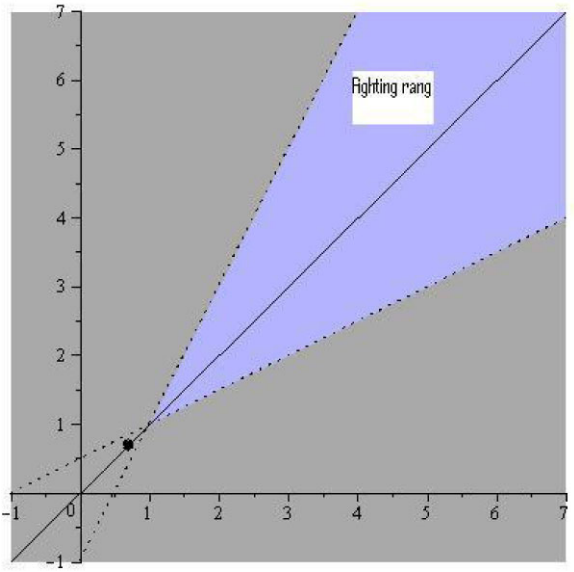

Fig. 9 Bifurcation diagram. *The horizontal axis* is the carrying level of E-cadherins of the cell 1, and *the vertical axis* is the carrying level of E-cadherins of the cell 2. To illustrate, the combined parameter $\frac{(s_1+s_2)l}{\alpha}$ is taken to be a constant. For example, $\frac{(s_1+s_2)l}{\alpha}$ is set to be 1 here. One bifurcation point is in the diagonal, *the big black point*. Below this point in the diagonal, two germline stem cells coexist peacefully, while above it, they will strongly push each other. In the "fighting range," above the diagonal, the cell 2 will push the cell 1 out of their niche, while below the diagonal, the cell 1 will push the cell 2 out

6 Conclusions and Discussion

We present a simplified model for the competition of two germline stem cells for the niche occupancy in the same niche. To establish this model, a model for germline stem cell adhesion process has been proposed, which consists of a logistical equation for E-cadherins and a linear spring equation. Based on the model for germline stem cell adhesion process, the model for the competition of two germline stem cells consists of Lotka–Volterra type model for the competition of matching E-cadherins and the equation for two spring system, where the deformation of cells contributes competition coefficients and the difference of intensity of E-cadherins in two germline stem cells acts as external force to the spring system. The model is a coupled system of two nonlinear first order and one second order differential equations. By numerically solving the model and simulating the dynamics, it is observed that the model catches the basic biological phenomenon, can explain the data variation, and may recover the missing information in the discrete data in Jin et al. (2008). The model confirms the major results in Jin et al. (2008) that the germline stem cell that has a higher carrying level of E-cadherins on its surface will eventually have a larger contact area with its niche (it is measured by the extension of a cell in x space), and will have a higher possibility to push the other cell out of their niche. Since each niche with two germline stem cells has its own dynamics of competition, the model may also offer an explanation to the oscillation pattern in discrete data at population level. The model predicts that there is a coexistence of two germline stem cells for two stem cells with the same carrying level of E-cadherins on their surface. However, the model also predicts that even for these two germline stem cells with the same carrying level of E-cadherins there still is a case of one stem cell pushing out the other one out of their niche. This means that for two wild-type germline stem cells in the same niche there still is a possibility that one cell can push the other one out of their niche as

some parameter has a small change. This may offer a theoretical explanation for the stem cell quality control that a stem cell can push another stem cell that accidentally changes its properties (some parameters).

More subtly, the model may recover some missing information in the discrete experimental data. The competition of two germline stem cells for the niche occupancy is mediated by E-cadherins. The biological experimental results seem to reveal that there is a correlation between the intensity of E-cadherins on the surface of the germline stem cell and the contact area between the germline stem cell and its niche. However, each data set measured at the same time point has a big range of variation among different niches. A deep dynamics needs to be recovered. Our model discovers that the intensity of E-cadherins and the contact area of the germline stem cell are not linearly related to each other, and it is a nonlinear relation and oscillates in time. Each niche may have its own specific biological parameters, for instance, the E-cadherin increasing rate r, Young coefficient s, the carrying level of E-cadherins, therefore, has its own dynamics and time scales. The measurements taken over different niches may have different states because of oscillations even at the same time. Therefore it is expected that there is a big range of variation in a data set.

It is clear that the models we present here are first approximations, rough and simplified models. There are several important issues which we do not consider or we need to modify. For example, a real germline stem cell is not a spring. Although many mechanical experiments reveal that a cell behave like an elastic material, treating a cell as a spring is only a rough approximation. Nevertheless, the models may be improved by considering a cell as a three dimensional spring in the current model framework. Secondly, the adhesion process involves biochemical interactions of E-cadherins. Our models only consider the intensity of E-cadherins instead of biochemical interactions. To include these biochemical interactions will require a new model, which must include the reaction diffusion process on the surface of a germline stem cell. Thirdly, modeling physical interaction between two germline stem cells is a real challenge for current mathematics and physics. There are many mathematical theories about elastic materials. However, we still do not have a complete understanding of the cell shape and its mechanics (Mofrad and Kamm 2006). Two cell physical interaction involves biophysical processes and biochemical interactions at molecular level while it involves the cell geometry and mechanics at cellular level. Although it is reasonable to model two cell physical interaction by using two spring system as a first approximation, a new idea is needed in the study of two cell physical interaction.

Mathematically, we present some basic analysis for the two models. It is well studied that the oscillation is forced by periodic external forces. Our model for germline stem cell adhesion process can be considered as an oscillation with an logistic external force. Most solutions will approach periodic solutions around the equilibrium point and more precisely, will approach periodic solutions in the center manifold given by the maximum force. As for the model for two germline stem cell competition, we have analyzed the equilibrium points and their stability, and we have found a pitchfork bifurcation for the intensity of E-cadherins. It may be important to study other parameters to see how they effect the whole dynamics. It may also be interesting to further the analysis we have done in the direction of global dynamics of the

model systems. For example, searching for a range of model variables and parameters in which the model global behavior (trajectories) can be clearly described would be interesting. However, it will be challenging.

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