Motion of interfaces in biological systems

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Interfaces might be characterised by properties such as energy per unit area, speed, width and interaction with inhomogeneities which may impede or accelerate their motion. For example:

- Interfaces with large energies per unit are more likely to remain flat, because forming bulges is then expensive. Tumour fronts having large energies per unit area may thus be less likely to form protrusions that separate to form metastatic clusters [1].
- Interfaces which move quickly are desirable when the motion is shrinking a diseased area, e.g., an apoptosis front sweeping through unhealthy cells, but undesirable when the motion is growing a diseased region, e.g., a tumour front advancing into healthy tissue. Finite interfacial speeds will delay responses to stimuli. Details of interfacial motion can tip the balance in kinetic contests where the fastest-growing phase 'wins' and becomes dominant at the expense of slower-growing phases [2].
- Interfaces are unlikely, in general, to be advancing through uniform tissue. Inhomogeneities will locally snag or 'pin' an interface, or accelerate its motion. Besides changing the overall speed of the interface, localised pinning and acceleration can cause bowing.
- Interfaces are unlikely to be impeded by features which are narrower than the interface itself. Thus broad, diffuse interfaces are less likely to be pinned.

Figure 1 is a sketch of a generic interface advancing through tissue. There are two pinning sites 'X' where the interface is pinned and one site 'Y' where it is accelerated. For the case of a tumour front 'X' might be an inclusion of especially dense tissue, whilst 'Y' might be a weakness in the healthy tissue such as a gap junction, or a site in the extra-cellular matrix where tumour cells can grip and exert strong tractive forces. Local pinning and acceleration make the interface bow, but there is a counteracting flattening effect from minimising interfacial energy.

Figure 2 shows how bowing, in this case facilitated by a pair of pinning sites, might help metastatic clusters separate from the surface of a primary tumour. Multiple metastatic clusters may emerge from the same section of interface.

Figure 3 shows a simple interfacial stability analysis for an interface between a tumour and surrounding tissue. It considers competition between cellular tractive forces pushing to form a bulge in the interface and interfacial energy effects tending to flatten it. When forces pushing to expand the bulge are dominant the interface is unstable and metastasis may result.

Figure 4 shows how the size of an escaping metastatic cluster may depend on the energy of the interface between the tumour and surrounding tissue. For small interfacial energies single cells can escape. For larger interfacial energies separation may be possible only for

clusters which consist of multiple cells moving together. Metastatic escape from such primary tumours may be inhibited until cells acquire cohesive traits.

Figure 5 shows how the work required to form a protrusion of critical size might depend on the energy per unit area of the interface between tumour and surrounding tissue. For larger interfacial energies angiogenesis and delivery of nutrients via the bloodstream will likely be needed to fuel the necessary work.

Figure 6 shows how a pinning site which is impeding passage of an advancing membrane can be enveloped within a liposome and left in the membrane's wake. The impact of such envelopment depends on the nature of the pinning site. In general, a membrane which is passing through an inhomogeneous medium will form both protrusions, which encourage exocytosis, and indentations, which increase the likelihood of endocytosis.

Figure 7 shows an apoptosis front advancing into diseased tissue. It illustrates some factors which may, in general, affect a kinetic contest between apoptosis and disease. The apoptosis front might initially advance fast enough to suppress disease, but slow beneath that threshold when its progress is curtailed by a need to generate replacement cells.

Figure 8 illustrates possible spontaneous synchronisation of cell cycles within clusters or domains [3]. It shows two domains within which cell cycles are synchronised. Here interfaces take the form of domain boundaries between regions where cell cycles are synchronised and regions where they are unsynchronised, or regions where they are synchronised albeit with different phases or angular speeds. The domains in figure 8 are delineated by domain boundaries, and surrounded by cells whose cycles are not synchronised. Motion of the domain boundaries is associated with domains variously growing, shrinking, morphing and moving. Motion of domain boundaries may cause cells to join, leave or re-join domains. These transitions will be hindered if domain boundaries are pinned by inhomogeneities.

Coupling between cell cycles might happen in tissue which is inflamed in response to infection or damage, when cells exchange paracrine factors with their neighbours.

It is healthiest for cell cycles to not be spontaneously synchronised, if synchronisation causes damaged cells to be swept unimpeded through the G1/S and G2/M checkpoints. Failing that, it is better for cells to belong to a slowly-cycling domain than one which is cycling rapidly. Thus, it is advantageous for domain boundaries to move in ways that eliminate and shrink domains, especially ones having large angular speeds.

I am very happy to acknowledge Muffin's contribution to this series of biology-themed papers.

References:

1. https://doi.org/10.6084/m9.figshare.9947135.v5
2. https://doi.org/10.6084/m9.figshare.8311703.v2
3. https://doi.org/10.6084/m9.figshare.4989719.v3
4. C.A.M La Porta and S. Zapperi, "The Physics of Cancer", Cambridge University Press, ISBN-13: 978-1107109599, 2017.

Figure 1

An interface advancing through tissue. There are two pinning sites 'X' where the interface is impeded and one site 'Y' where it is accelerated. For the case of a tumour front 'X' might be an inclusion of especially dense healthy tissue, whilst 'Y' might be a weakness in the healthy tissue such as a gap junction, or a site in the extra-cellular matrix where tumour cells can grip and exert strong tractive forces. Local pinning and acceleration make the interface bow, but there is a counteracting flattening effect from minimising interfacial energy.

Figure 2

Closely-spaced pinning sites can aid bowing of an interface between a growing tumour and surrounding tissue, and so promote metastasis. Figure 2(a) shows an interface in contact with pinning sites. Figure 2(b) shows the sites anchoring a protuberance which can grow, then separate. Figure 2(c) shows the resulting metastatic cluster.

A section of interface pinned in this way can cycle repeatedly through the sequence 2(a) => 2(b) => 2(c) => 2(a), causing multiple metastatic clusters to emerge from the same section of interface.

We model the situation sketched in this figure by considering a circular region of interface which has radius R and energy per unit area σ. We assume that the circle is surrounded by pinning sites which impede advance of the tumour front. A protrusion advancing through the circular gap in the manner of figure 2(b) must overcome the pressure exerted by the curved interface. In this model the pressure increases as the protrusion grows, attains a maximum of σ/R when the protrusion is a hemispherical cap with radius R, then diminishes again as the protrusion expands further. The work needed to attain the state of maximum pressure is $\pi R^2 \sigma$. Small metastatic clusters must overcome greater pressures in order to grow and escape, but can perhaps travel more easily through a body to seed new tumours.

Figure 3

A simple interfacial stability analysis for a hemispherical protrusion of radius r, in an interface between a primary tumour and surrounding tissue. In this analysis f_{tv} is the (possibly collective) cellular traction force per unit volume, whilst σ is the energy per unit area of the interface between the primary tumour and surrounding tissue.

The outward pressure attempting to grow the protrusion is $f_{tv}r/3$. This pressure is caused by the traction forces of cells in the protrusion attempting to escape from the surface of the primary tumour. The inward pressure attempting to shrink and flatten the protrusion is $-\sigma/r$. This pressure derives from the energetic cost of the increased interfacial area between the tumour and the surrounding tissue. Other pressure terms, e.g., ones caused by mechanical stress, are not considered in this analysis.

The two pressure terms are in balance when r is equal to $r^* = \sqrt{3\sigma/f_{tv}}$. When r < r* the flattening pressure dominates and the interface is stable. When r > r* expansion dominates and the interface is unstable. Instability may cause metastasis.

Figure 4

A sketch showing how the size of an escaping metastatic cluster might depend on the energy per unit area of the interface between tumour and surrounding tissue. In the model presented here $r^*/r_{cell} = \sqrt{3\sigma/f_{tv}r_{cell}^2}$, where r_{cell} is the radius of a tumour cell. For $\sigma < f_{tv}r_{cell}^2/3$ this ratio is less than one and lone cells can escape from the surface of a tumour, perhaps via an epithelial-mesenchymal transition. For $\sigma > f_{tv}r_{cell}^2/3$ escape may be possible only for clusters which consist of multiple cells moving together. This latter regime can help to explain observations that, in the majority of epithelial tumours, cancer cells form cohesive clusters that collectively invade the surrounding stroma [4]. Metastatic escape from such primary tumours may be inhibited until cells acquire cohesive traits.

Cluster sizes will be affected by the strengths of bonds between tumour cells, and between tumour cells and cells of surrounding tissue. These strengths will influence number of cells which can bind to form a cluster, and the value of σ.

There is an upper bound on the radius of a cluster, caused by a maximum limit on the number of cells which can combine to form that cluster. Small clusters might be better able to navigate narrow blood vessels, but large clusters may be more likely to survive the rigours of a journey from a primary tumour to a new, secondary site. Irrespective of cluster size, cells will seed a new tumour only if they exhibit an appropriate phenotype.

Figure 5

A sketch showing how E^*, the work required to form a protrusion with radius r = r*, might depend on the energy per unit area of the interface between tumour and surrounding tissue. In the model presented here $E^* = 3\pi\sigma^2/f_{tv}$. Energetic fluctuations may provide sufficient energy to perform this work for the smallest values of σ. Angiogenesis and delivery of nutrients via the bloodstream will likely be needed to provide the necessary energy at larger values of σ.

Figure 6

A sketch showing how a pinning site which is impeding passage of an advancing membrane can be enveloped within a liposome and left in the membrane's wake. In this scenario the pinning site might be stationary, or moving more slowly than the membrane. In general, a membrane which is passing through an inhomogeneous medium will tend to form both protrusions, which encourage exocytosis, and indentations, which increase the likelihood of endocytosis.

Figure 7

A sketch of four regions, containing cells in different states. The interfaces between regions can move from left to right. The regions contain, from right to left: healthy cells; diseased cells which are a risk to the organism; diseased cells that are being destroyed by externally-signalled apoptosis; healthy cells grown to replace ones destroyed by apoptosis. We postulate that the malfunctioning cells can be suppressed by externally-signalled apoptosis if $v_{apoptosis} > v_{infection}$, i.e., provided the apoptosis front advances sufficiently quickly that it can consume the diseased region. We suggest that the advance of the apoptosis front, and consequent elimination of errant cells, is sustainable only if $v_{replacement} >= v_{apoptosis}$, i.e., if damaged cells killed by apoptosis can be replaced in a timely manner with healthy new cells. An organism might employ alternative responses to cellular damage, e.g., senescence, if the apoptosis front cannot continue its advance. Senescence may be less effective than apoptosis at reducing the risk posed by errant cells, but unlike apoptosis it does not incur the expense of manufacturing replacement cells.

Cells which are rendered senescent for the kinetic reasons explained here might soon be removed by the immune system, once the tissue has returned to a steadier state.

Externally-signalled apoptosis could be effective in suppressing disease up to a maximum critical distance. The apoptosis front may initially advance fast enough to meet the condition $v_{apoptosis} > v_{infection}$ required for suppression, but slow beneath that threshold when its progress is curtailed by the need to generate replacement cells.

Figure 8

Two domains within which cell cycles are spontaneously synchronised. The two domains in figure 7 are delineated by domain boundaries, and surrounded by cells whose cycles are not synchronised. Motion of the domain boundaries is associated with domains variously growing, shrinking, morphing and moving. Motion of domain boundaries may cause cells to join, leave or re-join domains. These transitions will be hindered if domain boundaries are pinned by inhomogeneities.

Figure 1

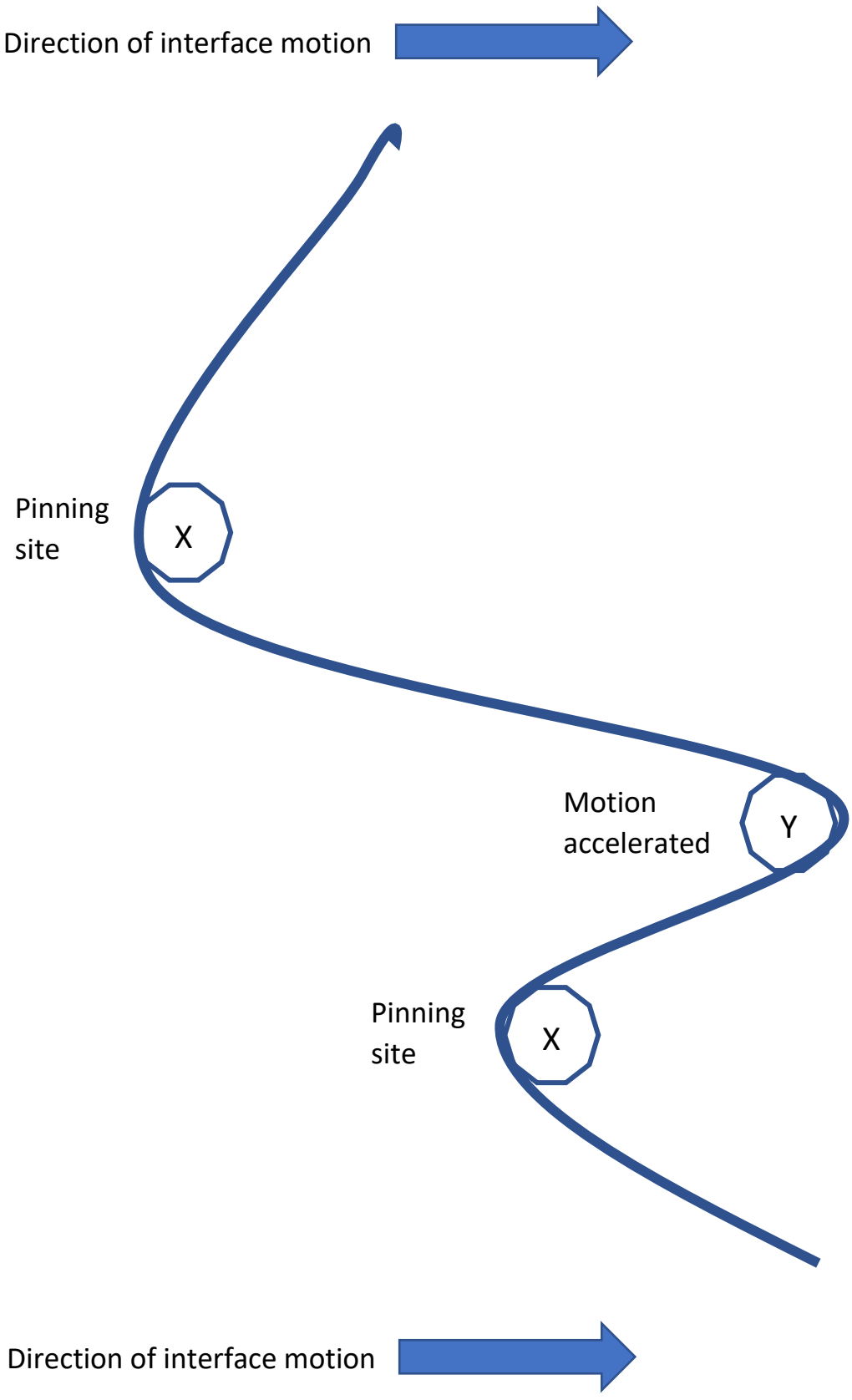

Direction of interface motion
Pinning site
X
Motion accelerated
Y
Pinning site
X
Direction of interface motion

Figure 2

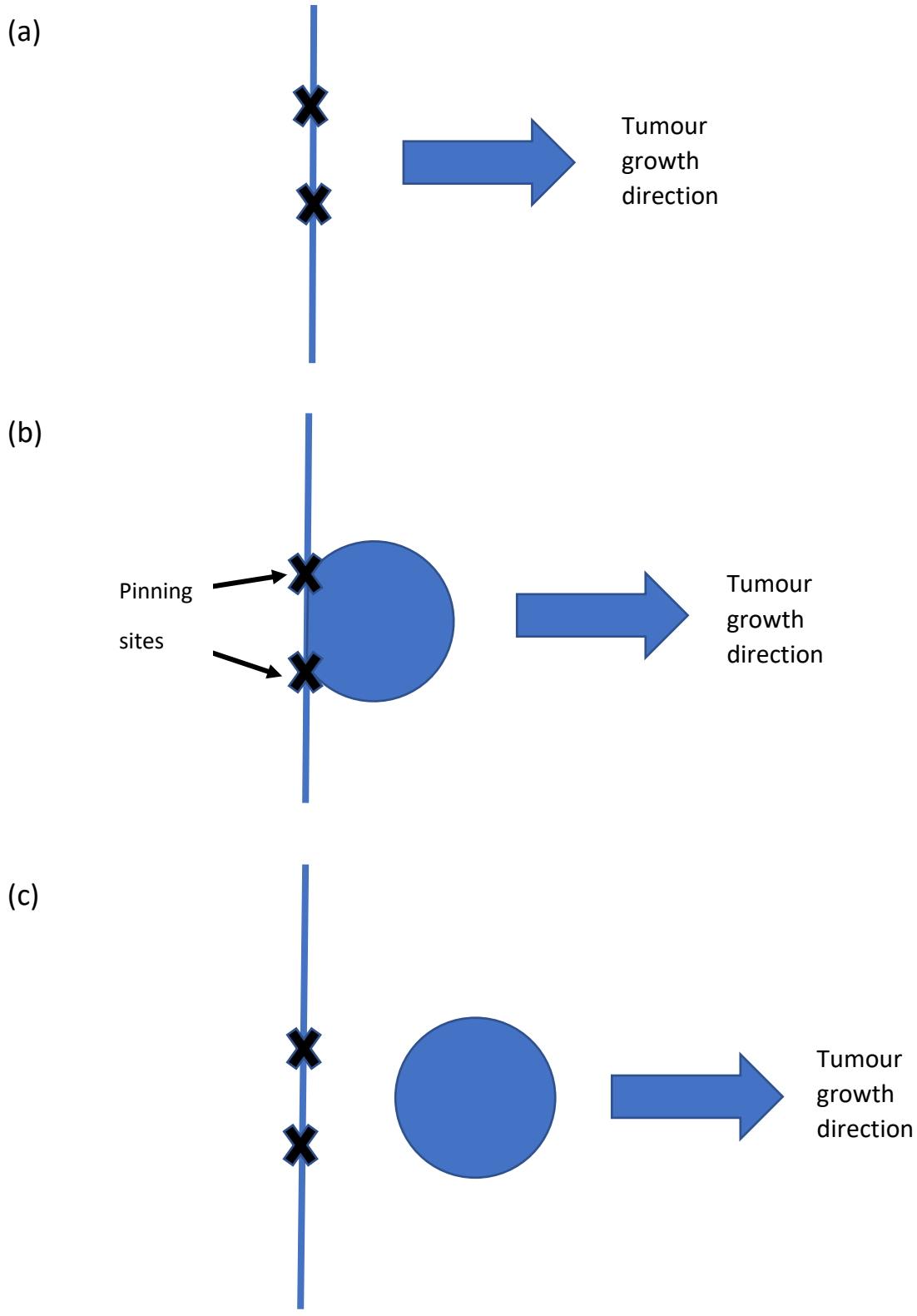

(a)
Tumour
growth
direction
(b)
Pinning
sites
Tumour
growth
direction
(c)
Tumour
growth
direction

Figure 3

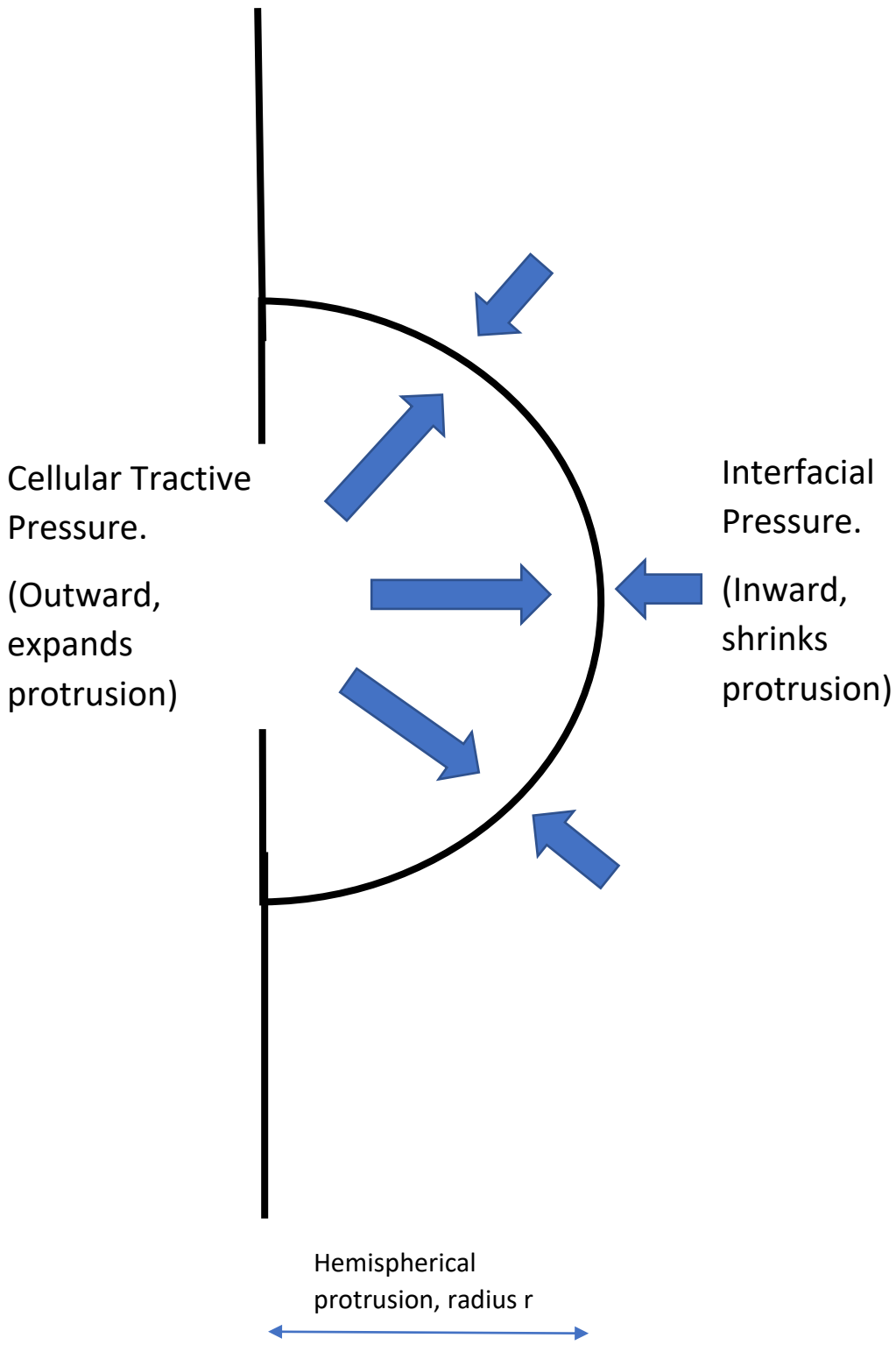

Cellular Tractive Pressure.
(Outward, expands protrusion)
Interfacial Pressure.
(Inward, shrinks protrusion)
Hemispherical protrusion, radius r

Figure 4

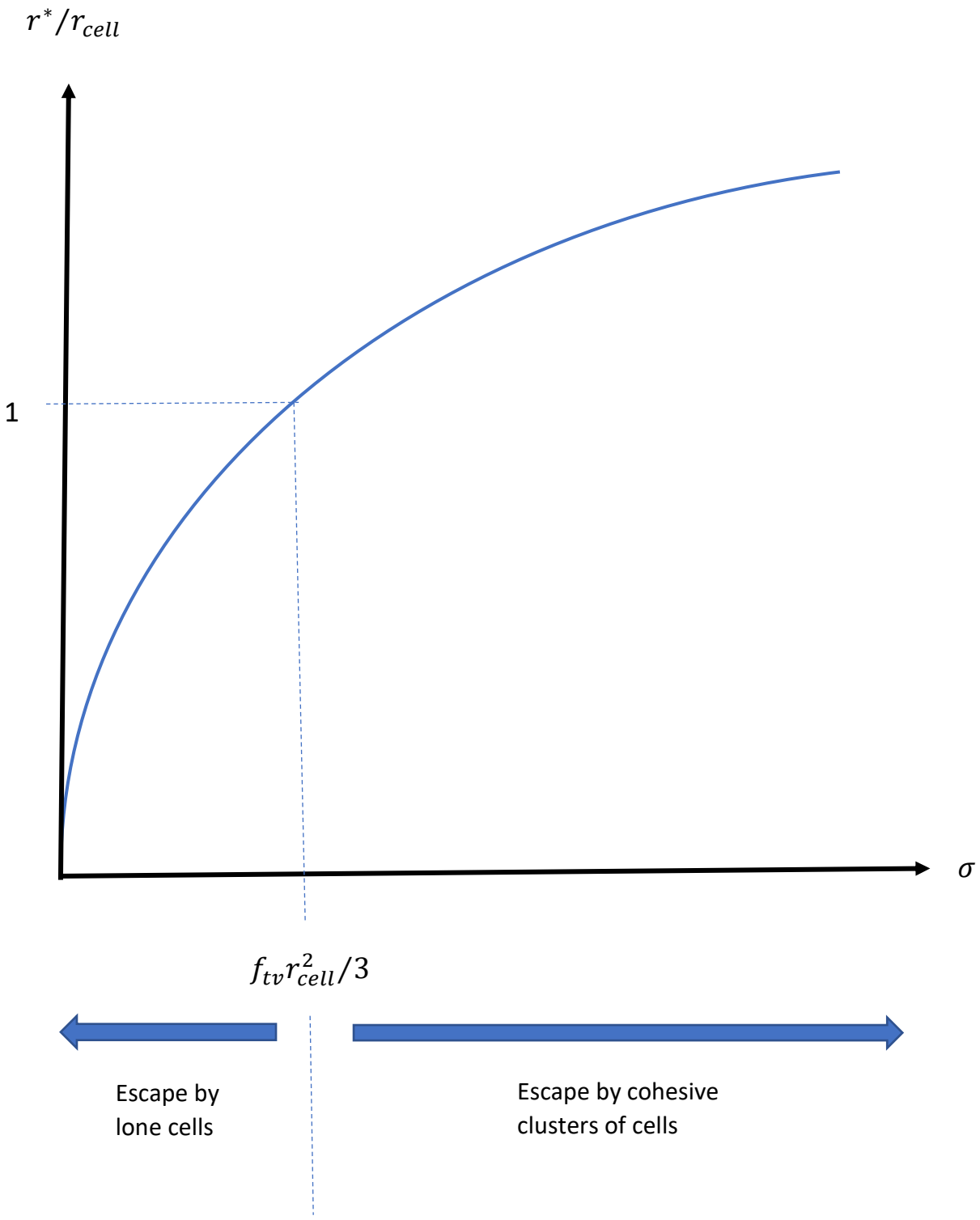

r^*/r_{cell}
1
σ
$f_{tv}r_{cell}^2/3$
Escape by lone cells
Escape by cohesive clusters of cells

Figure 5

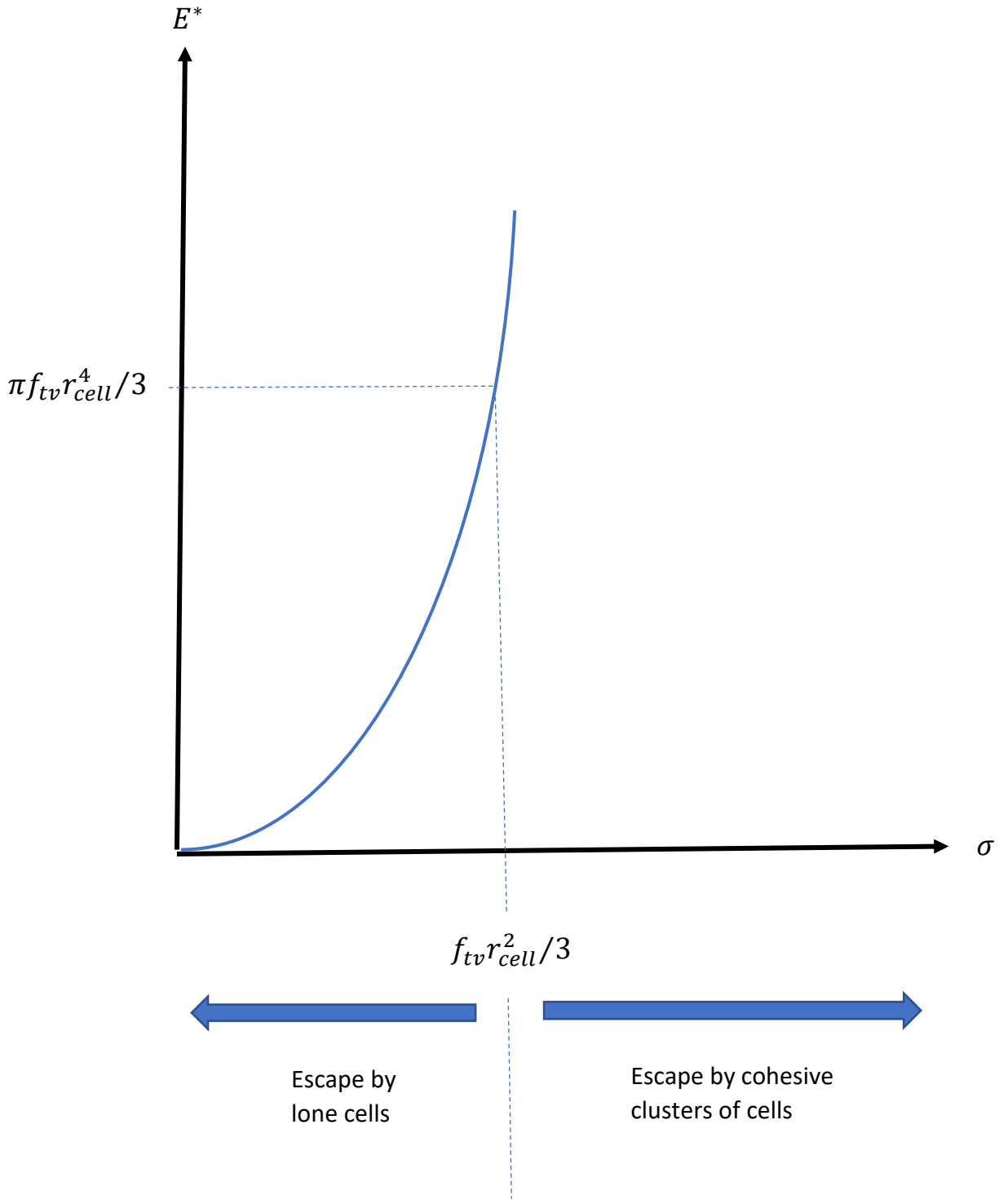

E^*
$\pi f_{tv} r_{cell}^4/3$
σ
$f_{tv} r_{cell}^2/3$
Escape by lone cells
Escape by cohesive clusters of cells

Figure 6

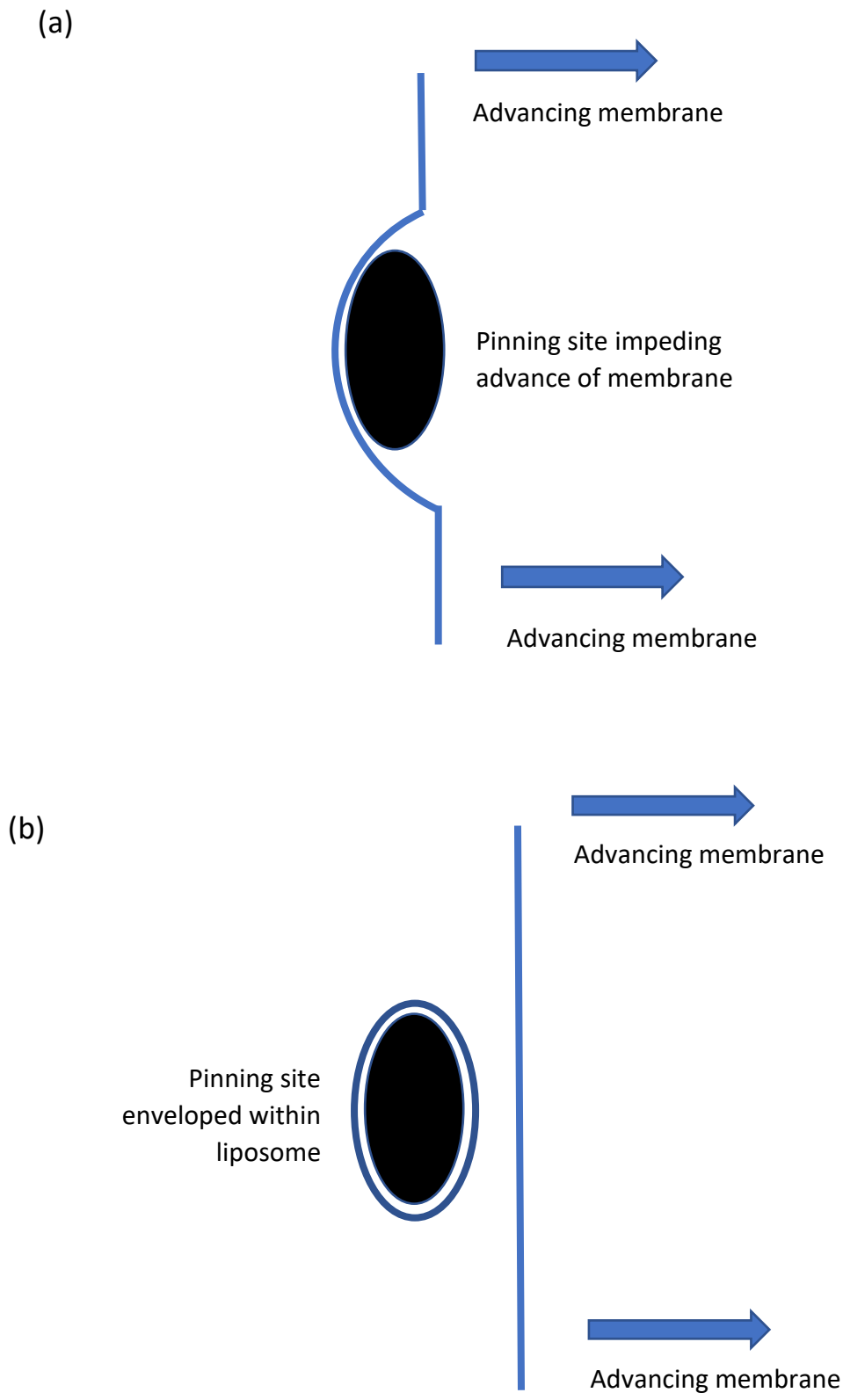

(a)
Advancing membrane
Pinning site impeding advance of membrane
Advancing membrane
(b)
Advancing membrane
Pinning site enveloped within liposome
Advancing membrane

Figure 7

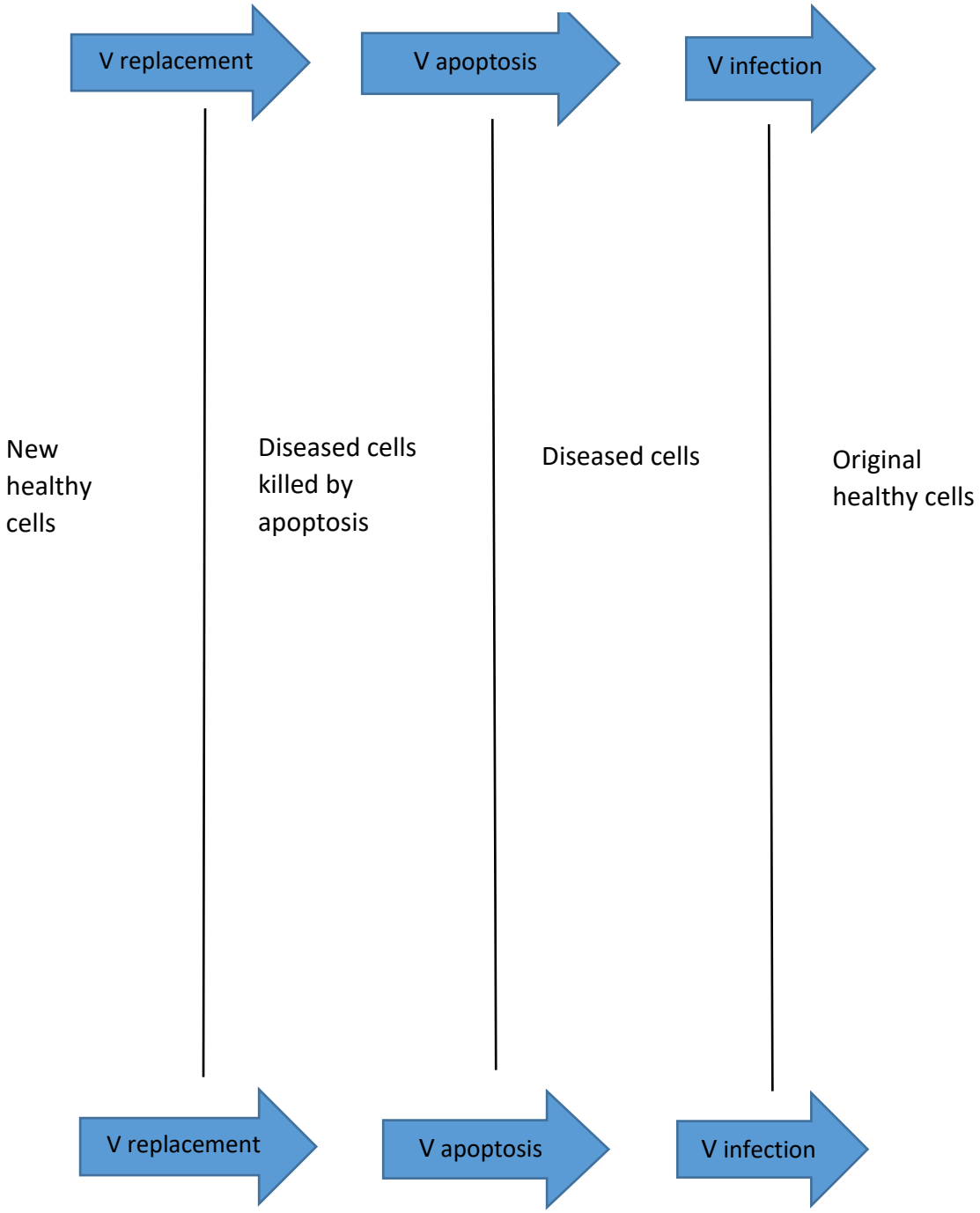
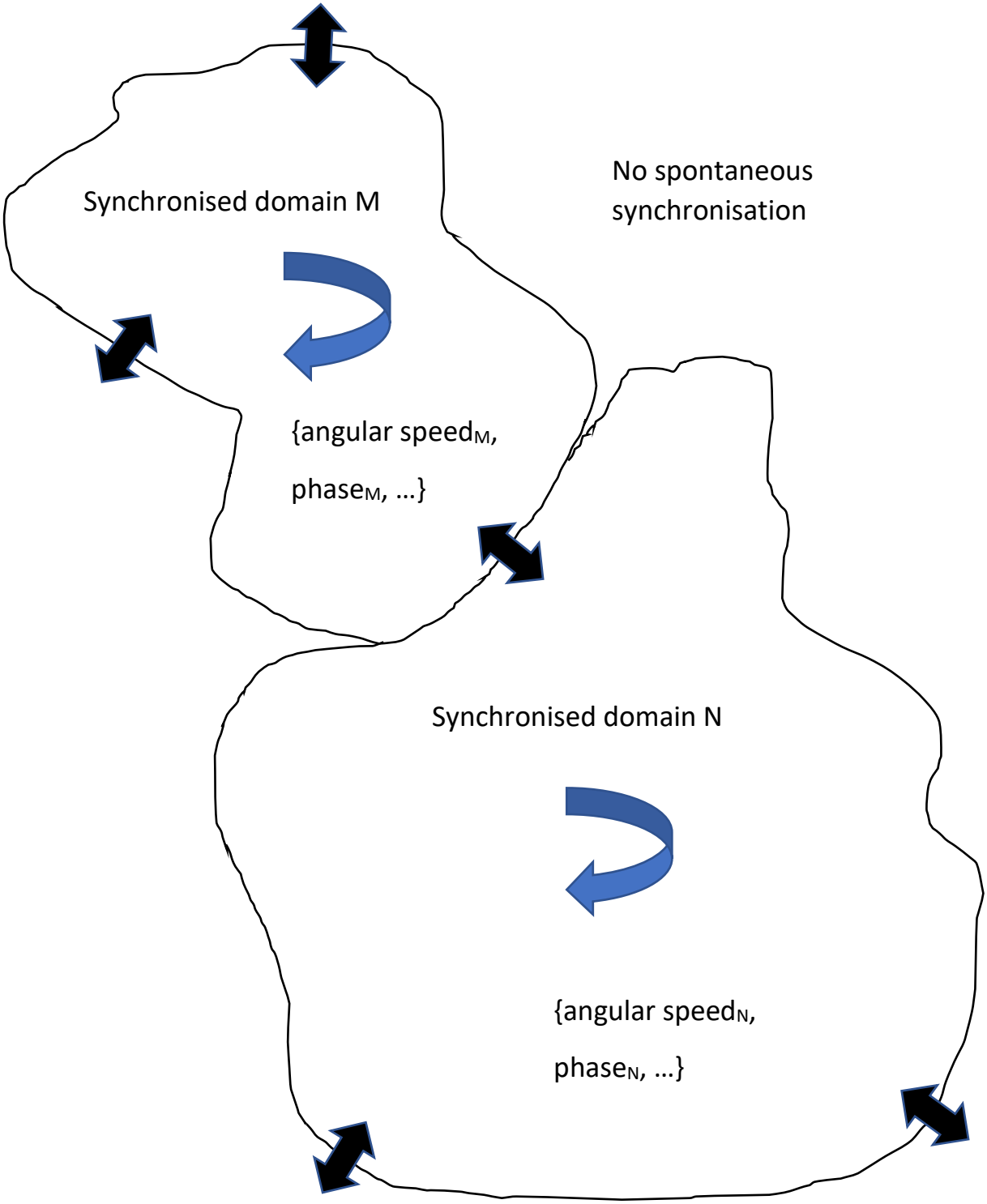

V replacement
V apoptosis
V infection
New healthy cells
Diseased cells killed by apoptosis
Diseased cells
Original healthy cells
V replacement
V apoptosis
V infection

Figure 8


Synchronised domain M
No spontaneous synchronisation
{angular speed$_M$,
phase$_M$, …}
Synchronised domain N
{angular speed$_N$,
phase$_N$, …}
No spontaneous synchronisation